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CONTENTS

THE WHOLE OF THE LITERARY MATTER IN THE LANCET IS COPYRIGHT

ADDRESSES AND ORIGINAL ARTICLES

A Virus in the Ætiology of Rheumatic Diseases. By G. HARDY EAGLES, M.D., and others 421

Hypospadias: Its Effects, Symptoms, and Treatment. By A. R. THOMPSON, F.R.C.S.—(*With diagrams*) 429

Sulphæmoglobinæmia: Its Cause and Prevention, with Special Reference to Treatment with Sulphanilamide. By H. E. ARCHER, M.R.C.S., F.I.C., and G. DISCOMBE, B.Sc. 432

Fatal Hæmatemesis and Melæna. By L. D. W. SCOTT, F.R.F.P.S. 435

Theophylline-Ethylenediamine in Cheyne-Stokes Respiration. By O. A. S. MARAIS, M.B., and J. MCMICHAEL, M.R.C.P.—(*Illus.*) 437

Response of the Pulse-rate to Exercise in Healthy Men. By A. BRADFORD HILL, D.Sc., and others—(*Illus.*) 441

Fluorescence Microscopy on Living Virus with Oblique Incident Illumination. By F. HIMMELWEIT, M.R.C.P. 444

NEW INVENTIONS

An Improved Vaginal Speculum. By S. JASWONSKY, M.D.—(*Illus.*). 449

REVIEWS AND NOTICES OF BOOKS

Physiological Basis of Medical Practice. By Prof. C. H. Best, M.D., and Prof. N. B. Taylor, M.D. 450

Diseases of the Colon and Rectum. By Prof. G. Schwarz, M.D., and others 450

Die Prophylaxe der Schlafstörung. By Dr. P. Vogler 451

Aids to the Treatment of Diseases of Children. By F. M. B. Allen, M.R.C.P. 451

Synopsis of Pediatrics. By Prof. J. Zahorsky, M.D. 451

Muir's Bacteriological Atlas. By C. E. van Rooyen, M.D. 451

Low Voltage Cathode Ray Tube. By G. Parr 451

Manual of Practical Anatomy. By Prof. J. E. Frazer, F.R.C.S., and R. H. Robbins, M.D. ... 452

A Textbook of Embryology. By Prof. H. E. Jordan, Ph.D., and J. E. Kindred, Ph.D. 452

Physiologie de l'innervation rénale. By J. Hamburger 452

LEADING ARTICLES

THE ORGANISATION OF A BLOOD TRANSFUSION SERVICE 453

THE NATIONAL CRIME-SHEET 454

ÆTIOLOGY OF CANCER OF THE BREAST 455

ANNOTATIONS

The Accuracy of the Medical Directory 456

Midwifery in Rural Areas . 456

Should the Eczematous Wash? 457

Illicit Traffic in Narcotic Drugs 457

A Change of Policy 458

Poisonous Umbellifers ... 458

Milk Curd and Infant Feeding 458

A Century of Corneal Transplantation 459

Lord Nuffield as Apothecary 460

Static Electricity in Operating Theatres 460

Paraganglioma 460

PUBLIC HEALTH

Steps Towards National Fitness—The L.C.C. Ambulance Service for Accidents—The Supply of Measles Serum—Valuable Labels 467

Infectious Disease in England and Wales 468

SPECIAL ARTICLES

Genetics of Cancer in the Mouse. By P. A. GORER, M.R.C.S. 461

British Medical Association: Section of Surgery: Obstructions of the Common Bile-duct 445

Section of Obstetrics and Gynæcology: Clinical Value of Prontosil and Similar Compounds in the Treatment of Puerperal Infections 446

Section of Diseases of Children: Enuresis—Tuberculous Cervical Adenitis 448

A Medical Congress in the Rocky Mountains 462

A Hunter Memorial—(*Illus.*) 463

Welfare of the Blind 464

Medicine and the Law: Manslaughter by Dangerous Driving 465

Ireland: The Milk Question 465

THE LANCET 100 Years Ago 474

CORRESPONDENCE

The Birth Stimulus and the Spawning Stimulus (Prof. J. H. Orton, D.Sc.) 469

"No Place for an Epileptic Boy" (Drs. J. Lloyd and J. N. Jacobson) 469

Pastoral Psychotherapy (Dr. F. Dillon, Dr. D. Hubble, Mr. A. B. W. Fletcher) 469

"Biochemical Control of Cancer" (Biochemist, Dr. R. Pakenham-Walsh) ... 470

Undesired Publicity (Mr. F. C. Goodall, Mr. F. W. Yeomans) 471

Tar or Just Dust? (Dr. J. Argyll Campbell) 471

THE SERVICES

Royal Naval Medical Service—Royal Army Medical Corps—Royal Air Force—Indian Medical Service—Deaths in the Services 471

GRAINS AND SCRUPLES

From F.R.C.S. (1936) (III) 466

PANEL AND CONTRACT PRACTICE

Refresher Courses—Another Dental Hæmorrhage 472

OBITUARY

John Gordon Thomson, F.R.C.P. 473

William Melrose Cumming, M.D. 473

MEDICAL NEWS

Medical Society of London 474

Chartered Society of Massage and Medical Gymnastics 474

Central London Throat, Nose, and Ear Hospital 474

North Devon Hospital 474

Fellowship of Medicine and Post-Graduate Medical Association 474

Société Internationale de Chirurgie 474

New Hospital for Halesowen 474

Rest Rooms at St. Bartholomew's 475

Wallsend Infirmary 475

Peasley Cross Isolation Hospital, St. Helens 473

Medical Charitable Society for the West Riding 473

INDEX NOTICE

THE LANCET, Vol. I, 1937 475

NOTES, COMMENTS, AND ABSTRACTS

"Chyrurgie Memoirs." By Enid Williams, M.D. .. 476

Recent Work on Pellagra .. 476

Healthy Holland 477

Studies in the History of Medicine 478

Cancer Research in Manchester 478

Appointments 475

Vacancies 475

Medical Diary 478

Births, Marriages, Deaths 478

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ADDRESSES AND ORIGINAL ARTICLES

A VIRUS IN THE ÆTIOLOGY OF RHEUMATIC DISEASES

BY G. HARDY EAGLES, M.D. Toronto, D.P.H.

P. R. EVANS, B.Sc., M.B., Ch.B. Manch., M.R.C.P. Lond.

A. G. TIMBRELL FISHER, M.C., F.R.C.S. Eng.

AND

J. D. KEITH,* M.D. Toronto

(From the Bacteriological Department, Lister Institute; Cheyne Hospital for Children; the Arthritic Unit, St. Stephen's Hospital; and King Edward VII Memorial Hospital for Children, Birmingham)

ALTHOUGH the possibility of a virus having some part in the causation of rheumatism had been considered by several investigators it was not until 1935, when Schlesinger, Signy, and Amies published the results of their researches on the virus ætiology of acute rheumatism that any support was given to this interesting hypothesis. In earlier work the attempt had been made to infect animals with material from rheumatic patients but convincing evidence of infectivity was not obtained. Recent advances in the study of viruses, particularly the use of the high-speed centrifuge in obtaining deposits of elementary bodies from virus-infected material and the examination of these particles with respect to their morphological characteristics and serological reactions led Schlesinger, Signy, and Amies to study acute rheumatism from this point of view. Relatively pure suspensions of bodies, morphologically similar to elementary bodies from known viruses, were obtained from rheumatic exudates and with these and sera from rheumatic patients agglutination tests were carried out. The technique was essentially that used in vaccinia and fowl-pox by Ledingham (1931), and in varicella by Paschen (1933) and by Amies (1933). These suspensions were specifically agglutinated by the sera of patients who were suffering from, and resisting, an acute rheumatic infection. Sera of normal persons and of patients suffering from various non-rheumatic infections failed to agglutinate the rheumatic suspensions. Suspensions of particles were obtained, also, from exudates of non-rheumatic patients, but these, while closely resembling the rheumatic bodies in stained films and by dark-ground illumination, remained unagglutinated by rheumatic sera. It was, therefore, suggested that the bodies found in pericardial exudates of patients suffering from acute rheumatism represented the actual infective agent of the disease.

These results opened up a number of interesting and important possibilities within the rheumatic group of diseases. It has frequently been suggested on clinical evidence that rheumatoid arthritis is in all probability closely related to acute rheumatic fever, their manifestations differing mainly in respect of degree and of age-group in which the infection occurred. Chorea has for some time been considered by most competent authorities as an evidence of rheumatic activity. It seemed possible that similar technical procedures would throw some light on the probable ætiology of rheumatoid arthritis and chorea and on the inter-relationships of the whole group, while at the same time extending and corroborating the work on rheumatic fever.

Preparation of Suspensions

It seemed reasonable to suppose that active and extensive inflammatory lesions, whatever their location in the rheumatic subject, should be a source of the causal agent. For this reason an extensive and varied search was made with acute rheumatic fever and rheumatoid material and, to some extent, with material from chorea.

I—ACUTE RHEUMATIC FEVER

(*a*) *Pericardial and Pleural Exudates.*—As a rule pericardial exudates were obtained at post-mortem from cases in the acute form with pericarditis and effusion. Only on rare occasions were they obtained ante-mortem. Pleural effusions were usually withdrawn during life. The necessary precautions for sterility were observed and only rarely were organisms present. Contaminating organisms were occasionally cultured but in such cases where the diagnosis of rheumatic fever was unquestioned streptococci were not found.

The fluids were taken into 3·8 per cent. sodium citrate solution to prevent clotting. The shortest possible time elapsed between taking and manipulation and whenever possible the specimens were kept in the cold room during that period.

A preliminary spinning at 3000 to 4000 rev. per min. removed cells and any fibrinous aggregations after which the supernatant fluids were subjected to centrifugation at 14,000 rev. per min. for one hour. This resulted in a very small plaque on the bottom of the tubes and an almost clear supernatant fluid. This was carefully removed and the deposit thoroughly triturated, using the etched end of a sterile glass rod. It was then thoroughly mixed with the fluid in which they were later to be suspended and redeposited at 14,000 rev. per min. This washed deposit was retriturated and mixed with suspending fluid and differential centrifugation at 3000 to 4000 rev. per min. carried out. The final supernatant fluid was removed and stored for morphological examination and serological tests.

This formed the basis of the preparation of all suspensions, additional manipulation, such as grinding with sand, being used only where the nature of the specimen called for it.

The most satisfactory fluid for suspensions was found to be saline to which 0·25 per cent. formalin was added, the particles remaining in even suspension over long periods. M/250 citric acid + disodium phosphate buffer *p*H 7·1, with NaCl added to 0·85 per cent., as used by Salaman (1937) for vaccinia, with the addition of 0·25 per cent. formalin, was also found satisfactory. In normal saline, spontaneous agglutination of the particles regularly occurred on standing in the cold room.

Suspensions from rheumatic exudates prepared in this way showed the typical bluish opalescence by direct illumination observed in suspensions of known virus particles.

(*b*) *Joint Fluids.*—These were taken from knee-joints at the height of inflammatory reaction and maximum effusion. Their subsequent treatment varied from that of pleural and pericardial exudates only in that owing to their highly viscous nature it was necessary to dilute them with at least twice their volume with saline or formol saline before centrifugation. Unless this was done no deposition of particles was obtained even at 14,000 rev. per min.

(*c*) *Blood Plasma.*—Since the route of infection in acute rheumatism is in all probability by the naso-pharynx, after which it becomes generalised, it seemed possible that at the height of primary infection the causal agent might be found in the blood

* Atholl-Moynihan Research Scholar, University of Birmingham.

stream. 25 to 30 c.cm. of blood was taken into citrate, and after removing the cells the plasma was treated exactly as exudates. Slight deposits were obtained, suspended, and examined.

(*d*) *Subcutaneous Nodules.*—These were removed as early after appearance as possible and, after macerating, were ground with sand, diluted with suspending fluid, and cleared of coarse material at 3000 to 4000 rev. per min. The supernatant fluid was then treated in the same way as other materials.

(*e*) *Cerebro-spinal Fluid.*—Cases showing evidence of widespread rheumatic infection were selected and the fluid examined in the usual way for virus bodies. About half the total number of fluids examined were obtained post mortem and yielded deposits, the amount of which have a direct relationship to the amount of cellular matter present, thereby giving an impression, which was confirmed on examination, that these consisted of very small cell particles.

(*f*) *Fibrin.*—The fibrinous exudate in fatal cases of typical "bread and butter" pericarditis was examined in two instances. After either preliminary grinding with sand or expressing in a tissue press, the exudate was diluted and centrifugalised. Deposits were obtained after prolonged differential centrifugation which resembled those obtained from ordinary exudates. This was not surprising, since the loose, fibrinous network contained an appreciable amount of fluid exudate. Owing to the fact that this form of pericarditis is found only in very acute cases it should have present large amounts of the infective agent.

(*g*) *Ascitic Fluid.*—This was examined in only one case in which ascites and general œdema were present. It is doubtful whether virus bodies were present, since high-speed centrifugation of 250 c.cm. yielded only a scanty deposit which agglutinated spontaneously.

(*h*) *Urine.*—Increased permeability of the kidney, as evidenced by a high Addis count, occurs frequently in active acute rheumatic fever. If it is assumed that at this stage virus bodies may be in the general circulation they might also appear in the urine.

Two cases were selected. In the first the Addis (1925) count was as follows: casts, 3000; W.B.C. and epithelial cells, 36 million; R.B.C., 4 million; protein, 30 mg. The second showed the following count: casts, 35,000; W.B.C., 11,700,000; R.B.C., 8,800,000; protein, 30 mg.; urea clearance, 91 per cent. Both cases were in a highly active stage as evidenced by acute carditis, active arthritis, and nodule formation.

After removing cellular matter, the urine was centrifugalised at 14,000 rev. per min. In both instances a very minute deposit was obtained and suspended.

II—RHEUMATOID ARTHRITIS

(*a*) *Joint Fluid.*—When possible early acute cases were selected in which joint fluid was in excess, with marked pain and swelling, but before secondary joint changes had occurred. Some degree of elevation of temperature was generally present and the erythrocyte sedimentation-rate increased. This type of case appeared more likely to show the presence of the infective agent than the more chronic types in which secondary tissue changes have supervened. When the disease was well established with hypertrophy of the synovial membrane and fibrinoid degeneration fluid was obtained at arthrotomy. The subsequent examination of these fluids did not vary from that of joint fluids from rheumatic fever.

(*b*) *Synovial Membrane.*—Hypertrophied membrane was removed by synovectomy in the course of operative treatment of suitable cases (Timbrell Fisher 1937). After mincing, grinding with sand, and suitable dilution, coarse particles were removed in the centrifuge at 3000 to 4000 rev. per min. and the supernatant fluid spun at 14,000 rev. per min. The deposit was thoroughly washed. After differential centrifugation a uniform suspension was obtained. In a number of cases the supernatant fluid was filtered through a Berkefeld "V" candle before high-speed centrifugation and in most instances the minced membrane was frozen and thawed six times before grinding.

As was expected, copious deposits were thrown down by high-speed centrifugation, and from these, uniformly dispersed suspensions of particulate matter could be readily prepared.

III—CHOREA

Cerebro-spinal fluids from typical cases of chorea were examined for the presence of bodies similar to those found in rheumatic material. In only one instance could these be demonstrated and a suspension procured. The fluid was withdrawn post mortem from a child of eight years with a history of severe chorea for six months. No history of rheumatic fever was present either in the patient or her family. Severe carditis and subcutaneous nodules were present. The fluid was bacteriologically sterile.

IV—EXAMINATION OF CONTROL MATERIAL

Pericardial and pleural fluids were obtained from cases of tuberculosis, carcinoma, cardiac failure without rheumatic history, and infections of known bacterial ætiology. Joint fluids were procured from simple traumatic injury such as torn semilunar cartilage and from such non-rheumatic conditions as tuberculosis and osteomyelitis. Synovial membrane was obtained from knee-joints with torn semilunar cartilages. These were treated in precisely the same way as material from rheumatism.

When such specimens were from infective sources suspensions of numberless small particles could be prepared. This was not surprising since such fluids must contain large quantities of cell granules and other products of cellular disintegration. Normal synovial membrane, when minced and ground, also yielded suspensions of similar particles. But simple transudates into the pleural or pericardial cavities yielded on high-speed centrifugation at best only scanty deposits not comparable in amount with those from pathological exudates. No deposits were obtained from normal joint fluids.

Examination of Suspensions

MICROSCOPIC

Two methods were used—dark-ground illumination and stained film preparations.

When a drop of suspension from rheumatic material was examined by dark-ground illumination and a magnification of 1000 diameters, numberless, evenly dispersed, very small particles were seen. Some difference in size and refractility was observed but the majority of the particles were, as nearly as could be determined by this method, of uniform size and conformed in every way to the description given of them by Schlesinger, Signy, and Amies. The larger, more opaque, bodies may represent some phase in the development of the virus if it is assumed that virus is present, or they may merely be the product of cellular disintegration. In favour of this latter view it may be significant that a preponderance of these larger forms was found in pathological exudates from non-rheumatic sources and in suspensions prepared from such tissue as synovial membrane.

Films were stained by Löffler's flagellar method, the modified techniques of Zettnow and Caesares-Gil and Morosow's modified Fontana Tribondeau silver impregna-

tion method. In these preparations particles of uniform size and staining could readily be identified. When films from control suspensions were examined in conjunction with those from rheumatism it was evident that particles closely resembling known virus bodies could be demonstrated in all suspensions, whether these had been prepared from rheumatic exudates, from joint fluids in rheumatic fever and rheumatoid arthritis, from synovial membranes, or from non-rheumatic control material. In some instances it was not possible to distinguish rheumatic suspensions from non-rheumatic. As a rule, however, a preponderance of bodies of uniform size and density was met with only in suspensions from rheumatic sources.

It must, therefore, be realised that on morphological grounds alone these particles cannot be said to have any definite diagnostic significance in rheumatism unless considered in conjunction with serological tests.

SEROLOGICAL INVESTIGATIONS

The microscopic agglutination test, using hanging-drop preparations in an aluminium ring moist chamber, was employed.

Mixtures consisting of equal volumes of suspension and dilutions of the sera to be tested were set up, left at room temperature, and examined at intervals of two to five days. For this purpose transmitted light with a 16 mm. objective and a × 10 ocular was used. Each suspension was tested with sera from cases of the same type of rheumatism from which it had been obtained and with sera from other types. Controls of normal and non-rheumatic sera were included and control suspensions were set up with normal sera and sera from the rheumatic group.

A positive reaction was indicated by the presence of small, irregularly shaped, highly refractile floccules. These commonly were present on the first or second day, but occasionally did not appear until later. The absence of agglutination was shown during the first forty-eight hours by a clear drop, and later by the suspension settling out on the bottom of the drop in a thin plaque which presented an even ground-glass appearance. This was invariable with controls and was used, in addition, as an index of suitable density of the suspension.

As an additional control, agglutinated and unagglutinated suspensions were from time to time examined by dark-ground illumination, when the presence or absence of floccules was confirmed.

SUSPENSIONS EMPLOYED

Table I contains a list of the suspensions from rheumatic fever, rheumatoid arthritis, chorea, and from non-rheumatic sources, which were tested with appropriate sera. These were chosen to cover as wide a range of material and rheumatic activity as possible. The agglutination of these suspensions by sera from acute rheumatic fever, rheumatoid arthritis, and chorea is indicated. The failure of these sera to agglutinate the control suspensions is also shown. In many instances the amount of suspension obtained from joint fluids, plasma, and subcutaneous nodules was too small or of insufficient density to permit of their use as antigens.

SERA

These were selected to include patients suffering from rheumatism of various types—acute rheumatic fever, acute, subacute, and chronic rheumatoid arthritis, chorea with and without carditis, and an occasional case of Still's disease. The rheumatic fever group included the disease in all stages, although the majority were in the active stage, with evidence of widespread infection such as carditis, pericarditis and subcutaneous nodules, pyrexia, and increased erythrocyte sedimentation-rate.

A control group of sera (see Table V) was studied at the same time. This included cases of widely differing clinical diseases, but excluding those with any history of rheumatism. A number of sera were selected on the basis of high erythrocyte sedimentation-rate, although Schlesinger, Signy, and Amies had already pointed out that this feature alone was not correlated with positive agglutination of rheumatic suspensions. In this group was included also sera with a very strongly positive Wassermann complement-fixation reaction and a number from pyrexial states of non-rheumatic origin.

TABLE I

Suspensions tested for Agglutination

Number of suspension.	Material from which suspension was prepared.	Disease.	Agglutination with serum from—		
			RF.	RA.	Uncomplicated chorea.
1	Pc. fluid.	Fatal RF.	+	+	+
2	"	"	+	+	+
3	Fibrin from pericardium.	"	+	..	..
4	Pc. fluid.	"	+	..	..
5	"	"	+	..	..
6	Fibrin from pericardium.	"	+	..	..
7	Pc. fluid.	"	+	..	+
8	"	"	+	+	..
9	"	"	+	..	..
10	Joint fluid.	RF.	+	..	..
11	Pleural fluid.	"	+	..	+
12	"	"	+	..	..
13	"	"	+	..	..
14	Joint fluid.	Early RA.	+	+	..
15	"	"	..	+	..
16	"	Subacute RA.	+	+	..
17	Joint washings.	Chronic "	0	..	..
18	Synovial membrane.	Subacute "	..	+	..
19	Cerebro-spinal fluid.	Chorea with carditis and nodules.	+	..	+
20	Pc. fluid.	Terminal effusion; intestinal hæmorrhage; cor bovinum.	0*	..	..
21	"	Bacterial endocarditis.	0	..	..
22	Pleural fluid.	Tuberculous pleurisy.	0	..	..
23	Pc. fluid.	Hyperpietic heart failure.	0	..	..
24	Vaccinia.	Suspension from lapine.	0	..	..

+ = Agglutination occurred.
0 = No agglutination with known positive sera.
Dots under agglutination = no test made.
* Positive with one rheumatic fever serum but negative with another known positive serum.
Pc. = pericardial; RF. = rheumatic fever; RA. = rheumatoid arthritis.

Almost all sera were filtered before use. Some substance, possibly lipoid, was encountered in the great majority of sera from rheumatism which gave rise to floccules in the hanging-drop preparations and either masked or confused the reading of agglutination. Sera were filtered through small size L_2 Chamberland candles, both having previously been chilled in ice. This procedure proved effective,

TABLE II

SHOWING CLINICAL CONDITION AND AGGLUTINATION IN CASES FROM WHICH SINGLE SPECIMENS OF SERUM WERE OBTAINED, OR FIRST SPECIMENS, WHERE SEVERAL WERE OBTAINED FROM SAME CASE

No. of serum.	Age.	Previous attacks.	Pains.	Joint swelling.	Active carditis.	Nodules.	Chorea.	Tachy-cardia.	Pyrexia.	Blood sedimentation.	Clinical notes.	Agglutination of suspensions from—		
												RF.	RA.	Chorea (C.S.F.).
GROUP 1.—ACTIVE RHEUMATISM WITHOUT CARDITIS OR CHOREA														
1	11	0	+	+	0	0	0	..	..	78/200	Sore-throat 4 weeks before.	1/16	0	..
2	8	+	0	0	?	0	0	+	+	..	Pleurisy with effusion.	0	..	..
3	9	+	0	0	0	+	0	0	0	..	No evidence carditis at this time.	1/16	1/16	..
4	14	0	+	+	0	0	0	+	+	..	Sore-throat 9 days before.	0	0	..
GROUP 2.—ACTIVE RHEUMATISM WITH CARDITIS														
5	9	+	0	0	?	0	0	+	+	..	Recurrence.	0	..	..
6	20	+	0	0	+	0	0	..	..	100/200	Sore-throat 5 weeks before.	0	..	..
7	7	+	+	+	+	+	0	+	+	..	..	0	..	..
8	11	0	+	+	+	0	0	+	+	..	..	0	..	..
9	24	+	+	0	+	0	0	..	..	..	Recent pericarditis.	1/8	..	..
10	8	0	0	0	+	0	0	0	0	20/200	Sore-throat 2 weeks before.	1/16	1/8	..
11	12	+	..	..	+	0	0	+	0	..	Pericarditis.	1/4	1/4	1/4
12	8	+	0	0	+	0	0	+	0	21/100	..	0	0	0
13	10	+	0	0	?	0	0	0	+	18/100	..	0	..	..
14	5	+	0	0	+	0	0	+	0	..	Sore-throat 1 week before.	0	0	..
15	16	+	+	0	+	0	0	+	0	..	" "	1/4	..	..
16	..	..	..	..	+	..	..	..	..	..	Full notes not available.	0	..	..
17	..	+	0	0	+	0	0	+	0	42/200	Sore-throat 4 days before.	1/8	..	..
18	14	0	+	+	+	0	0	+	+	..	Pericarditis.	1/32	1/16	..
19	9	+	+	0	+	0	0	+	+	46/100	Sore-throat 1 week before.	0	..	..
20	9	0	+	0	+	0	0	0	0	..	" "	1/16	..	..
21	13	+	0	0	?	0	0	+	+	125/200	..	0	..	..
22	11	+	0	0	?	+	0	+	..	2/100	Congestive failure.	1/8	..	..
23	9	0	0	0	+	0	0	+	+	..	Sore-throat 1 week before.	1/32	1/16	1/4
24	14	+	0	0	+	0	0	0	0	120/200	Recovering pericarditis.	0	0	0
25	10	+	+	0	+	+	0	+	+	35/200	..	1/32	1/32	..
26	8	0	0	0	+	0	+	+	0	..	..	0	0	..
27	8	0	0	0	+	0	+	+	0	..	..	0	..	..
28	10	0	0	0	+	0	0	+	0	51/200	Sore-throat 1 week before.	0	..	..
29	10	+	0	0	?	0	0	0	0	15/100	Convalescent; ? still had carditis.	0	..	..
30	13	0	0	0	+	+	0	+	+	25/100	Sore-throat 4 days before.	1/8	..	..
31	7	+	0	0	+	+	0	..	..	33/100	..	1/4	..	..
32	10	+	0	0	+	0	0	+	+	45/100	Sore-throat 4 weeks before.	1/16	..	..
33	12	0	0	0	+	0	+	..	..	..	..	0	..	..
34	6	+	0	0	+	0	0	0	0	15/200	..	1/8	..	..
35	8	..	..	..	+	+	..	..	..	..	..	0	..	..
36	11	+	0	0	+	+	0	+	0	..	Sore-throat 2 weeks before.	1/8	0	1/16
37	12	+	0	0	+	+	0	..	..	..	..	0	..	..
38	8	0	0	0	+	+	0	+	0	..	..	0	..	..
39	6	+	0	0	+	0	0	+	0	..	..	0	..	..
40	5	0	+	0	+	+	0	+	+	40/200	..	1/4	1/4	..
41	7	0	+	+	+	0	0	+	0	..	Nephritis.	1/16	..	..
42	11	+	0	0	+	0	+	+	+	..	..	1/8	1/8	1/4
43	9	+	0	0	+	0	0	0	0	3/200	..	1/4	..	..
44	7	0	0	0	?	+	0	0	0	..	..	1/16	..	..

TABLE II—(*Continued*)

No. of serum.	Age.	Previous attacks.	Pains.	Joint swelling.	Active carditis.	Nodules.	Chorea.	Tachy-cardia.	Pyrexia.	Blood sedimentation.	Clinical notes.	Agglutination of suspensions from—		
												RF.	RA.	Chorea (C.S.F.).
45	12	+	0	0	?	0	0	..	..	25/100	..	0	..	..
46	9	0	0	0	+	+	0	0	0	20/100	..	1/32	..	..
47	6	0	0	0	+	0	+	0	0	16/100	..	0	..	..
48	11	0	+	0	+	0	0	0	0	60/100	..	1/16	..	..
49	11	+	+	0	+	+	0	+	+	20/200	..	0	0	..
50	8	+	0	0	+	0	0	0	0	25/200	Sore-throat 4 days before.	1/8	..	..
51	4	+	0	0	+	0	0	+	+	..	Congestive failure.	0	..	..
52	16	+	0	0	+	0	0	+	0	..	Pericarditis.	0	0	..
53	5	+	0	0	+	0	0	+	0	50/100	..	1/4	1/4	..
54	11	+	0	0	+	0	0	+	+	29/200	Sore-throat.	0	..	..
55	11	+	0	0	+	+	0	+	0	..	..	0	..	..
56	10	0	0	0	?	+	0	+	0	3/200	Congestive failure.	1/16	1/16	..
57	10	+	0	0	+	0	0	+	0	40/100	Sore-throat 3 days before.	0	..	..
58	4	0	0	0	+	+	0	+	+	20/100	..	1/16	..	..
59	13	0	0	0	+	+	0	+	+	..	..	1/16	..	..
60	8	+	0	0	+	0	0	0	0	15/200	..	0	..	..
61	14	+	0	0	+	0	0	+	+	..	..	0	..	..
62	12	0	+	0	+	0	0	0	0	40/200	Sore-throat 4 weeks before.	1/16	1/8	..
63	7	+	0	0	+	0	0	+	0	..	..	0	..	..
64	8	0	0	0	+	0	0	0	0	18/100	..	0	..	..
65	14	0	0	0	+	+	0	..	..	..	..	1/32	1/32	1/8
66	8	0	+	0	+	0	0	0	0	28/200	Sore-throat 1 week before.	0	..	..
67	11	+	0	0	+	+	+	+	+	..	..	0	..	..
68	..	..	..	..	+	..	..	..	..	..	Full notes not available.	1/16	..	..
69	9	+	0	0	?	+	0	0	0	..	..	1/16	1/16	..
70	10	0	+	0	+	0	+	+	0	..	..	0	..	..
71	11	0	+	+	+	+	0	+	0	12/200	..	0	..	..
							GROUP 3.—CHOREA ALONE							
72	7	0	0	0	0	0	+	0	0	..	..	1/4	..	..
73	6	0	0	0	0	0	+	0	0	5/200	..	0	0	..
74	6	0	0	0	0	0	+	0	0	..	..	0	..	..
75	12	0	0	0	0	0	+	0	0	..		1/16	1/8	1/8
76	8	0	0	0	0	0	+	0	0	..	..	1/8	..	..
77	8	0	0	0	0	0	+	0	0	5/200	..	1/8	..	..
78	8	0	0	0	0	0	+	0	0	7/200	Recent carditis.	1/16	..	..
79	8	0	0	0	0	0	+	+	0	..	..	0	..	..
							GROUP 4.—INACTIVE RHEUMATISM							
80	10	+	0	0	0	0	0	0	0	..	? Inactive several months.	0	..	..
81	..	+	..	..	..	..	..	..	..	..	Recovered from carditis.	1/16	..	..
82	9	+	0	0	0	0	0	0	0	6/100	Inactive 5 months.	1/4	1/4	1/4
83	8	+	0	0	0	0	0	0	0	2/100	„ 2 „	0	0	0
84	11	+	0	0	0	0	0	0	0	7/100	..	0	0	..
85	7	+	0	0	0	0	0	+	0	5/100	..	1/4	..	..
86	10	+	0	0	0	0	0	0	0	..	Inactive 1 year.	1/16	1/4	1/4
87	14	+	0	0	0	0	0	0	0	6/100	„ 2 months.	0	0	0
88	8	+	0	0	0	0	0	0	0	1/100	..	0	0	0

Blood sedimentation-rates in first hour = { over /200 by Westergren's (1921) method. / over /100 by Payne's (1932) method.

TABLE III

Showing the agglutination titres obtained with rheumatic fever sera taken at various stages during the clinical course in individual cases and suspensions (susp.) from rheumatic fever, rheumatoid arthritis, and chorea (C.S.F.)

Case.	Date of sample of serum.	Condition of patient.	Agglutination. RF. susp.	RA. susp.	Chorea susp. (C.S.F.).
18	24/2/36	Acute pc.; very ill.	1/32	1/16	..
	3/3/36	Acute pleurisy; very ill.	0	..	..
	12/3/36	Improving.	0	..	..
	19/3/36	"	0	..	..
	31/3/36	No definite signs of activity.	0	..	..
	14/4/36	Inactive.	0	..	..
	30/4/36	"	1/16	..	..
	21/5/36	"	0	0	0
8	13/3/36	Typical RF. with carditis.	0	..	..
	24/3/36	B.S.R. 30/200.	0	..	..
	2/4/36	Settling down.	0	..	..
	16/4/36 }	Painless joint effusions, W.R. +	0	..	..
	28/4/36 }	No active rheumatism.	1/8	1/8	..
25	25/5/36	Fever pains, carditis, nodules. B.S.R. 35/200.	1/32	1/32	..
	9/6/36	" 30/200.	0	0	..
	1/7/36	" 30/200.	0	0	..
	27/7/36	" 25/200.	0	..	..
16	3/11/36	RF.	0	..	..
	23/11/36 }	Clinical details not available. {	1/16	..	..
	5/12/36 }		1/4	..	..
	17/12/36 }		1/4	..	..
52	26/3/36	Cardiac cripple; acute pc.	0	0	..
	2/4/36	Fever and pericarditis still.	0	..	..
	16/4/36	" "	0	..	..
	28/4/36	No fever, pericardial rub.	1/16	1/16	..
23	8/5/36	Polyarthritis and carditis.	1/32	1/16	1/4
	29/5/36	No signs of activity.	0	0	..
	17/11/36	Nodules, recurrence of carditis, B.S.R. 16/100.	0	..	..
20	15/10/36	Carditis, first attack; B.S.R. 15/200.	1/16	..	..
	23/11/36	B.S.R. 4/200.	1/8	..	..
	19/12/36	Inactive.	1/16	..	..
36	1/5/36	Carditis and nodules following sore-throat.	1/8	0	1/16
	16/6/36	Nodules still present.	0	0	..
	1/7/36	" "	0	..	..
10	27/4/36	Carditis, first attack; B.S.R. 20/200.	1/16	1/8	..
	8/5/36	Recovering; B.S.R. 15/200.	1/8	1/4	1/4
	16/6/36	Well; B.S.R. 8/200.	1/8	0	..
62	27/4/36	Pains and carditis, first attack; B.S.R. 40/200.	1/16	1/8	..
	8/5/36	Improving; B.S.R. 30/200.	1/4	1/4	1/4
	9/6/36	Improving; B.S.R. 12/200.	0	0	..
42	8/5/36	Recurrence of carditis and chorea.	1/8	..	..
	9/6/36	About the same.	0	..	..
	9/7/36	Improving.	1/4	..	..
34	16/11/36	Soon after recurrence; B.S.R. 5/200.	1/8	..	..
	30/11/36	B.S.R. 25/200.	1/16	..	..
78	6/10/36	Uncomplicated chorea.	1/16	..	..
	23/11/36	Improved.	1/4	..	..
17	16/11/36	Recurrence of carditis; B.S.R. 42/200.	1/8	..	..
	30/11/36	Improving; B.S.R. 30/200.	1/16	..	..
49	25/5/36	Fever, pains, and carditis (recurrence); B.S.R. 20/200.	0	0	..
	1/7/36	..	0	0	..
7	16/12/35	Recurrence of arthritis, carditis, and nodules.	0	..	..
	21/9/36	Convalescent; nodules still present.	1/32	1/32	..
9	24/3/36	Recent pericarditis.	1/8	..	..
	1/4/36	B.S.R. 48/200.	1/16	0	..
1	29/4/36	First attack of arthritis; B.S.R. 78/200.	1/16	..	..
	16/6/36	Well; B.S.R. 6/200.	1/8	..	..
14	26/6/36	Recurrence of carditis.	0	..	..
	1/7/36	Improved; B.S.R. 10/200.	0	..	..
27	21/5/36	First attack of carditis and chorea.	0	..	..
	16/6/36	No signs of activity.	0	0	..
30	16/11/36	First attack of carditis and nodules; B.S.R. 25/100.	1/8	..	..
	8/12/36	No sign of activity, except B.S.R. 12/100.	1/16	..	..
31	15/2/37	Recurrence of carditis and nodules; B.S.R. 32/100.	1/4	..	..
	18/5/37	In statu quo; B.S.R. 33/100.	0	..	..
32	15/12/36	Recurrence of carditis; B.S.R. 45/100.	1/16	..	..
	2/2/37	Improving; B.S.R. 24/100.	1/8	1/8	..
40	1/7/36	First attack of pains, carditis, and nodules; B.S.R. 40/200.	1/4	..	..
	27/7/36	Improving; B.S.R. 25/200.	0	..	..
50	16/11/36	Recurrence of carditis; B.S.R. 25/200.	1/8	..	..
	30/11/36	Improving; B.S.R. 10/200.	0	..	..
58	15/12/36	First attack with fever, carditis, and nodules; B.S.R. 20/100.	1/16	..	..
	2/2/37	Slightly improved; no fever.	0	0	..
4	14/5/36	First attack, fever and polyarthritis.	0	..	..
	28/5/36	Well.	0	..	..

pc. = pericarditis.
.. = no test made.

although it was realised that some loss in titre probably took place. Withdrawal of blood during a fasting period was of little value in eliminating the lipoid-like substance, nor was high-speed centrifugation of the sera effective.

Cross-agglutination Tests

A certain proportion of acute rheumatic fever sera were put up with suspensions from rheumatoid arthritis and in a few instances with a suspension from cerebro-spinal fluid from acute chorea. Sera from acute chorea and rheumatoid arthritis were also set up with suspensions from acute chorea, rheumatoid arthritis, and acute rheumatic fever. By this means the presence of an antigenic factor common to the group of rheumatic diseases was examined.

It was realised early in the investigation that the most hopeful source of virus bodies in rheumatoid arthritis was joint fluid from acute cases. Such occur infrequently in hospital practice, and consequently the supply of suspension from this source was limited, and only a relatively small series of cases was available for test. Since only one suspension was obtained from chorea the number of tests in which it was employed was also limited.

Rheumatoid arthritis is a slowly progressive disease. It was, therefore, difficult to select periods in the clinical course when an immunity reaction was likely to be elicited. For this reason, it was considered that evidence of inter-relationship between acute rheumatic fever and rheumatoid arthritis would more readily be obtained if rheumatic sera were set up with rheumatoid arthritis suspension. The series examined on this basis contains a relatively large number of sera.

RESULT OF AGGLUTINATION TESTS

In Table II are shown the agglutination titres obtained, using sera from cases of acute rheumatic

fever and chorea with suspensions from rheumatic fever, rheumatoid arthritis, and chorea (C.S.F.).

Table III shows the agglutination titres obtained with rheumatic fever sera taken at various stages during the clinical course in individual cases and suspensions from rheumatic fever, rheumatoid arthritis, and chorea (C.S.F.).

In Table IV are set out the agglutination titres with rheumatoid arthritis sera and suspensions from rheumatoid arthritis and rheumatic fever.

TABLE IV

Showing the agglutination titres obtained with rheumatoid arthritis sera and suspensions from rheumatoid arthritis and rheumatic fever

No. of serum.	Age of patient (years).	Length of history.	Arthritis.	Pyrexia.	Blood sedimentation.	Clinical notes.	Suspension.	
							RA.	RF.
138	7	1 mth	+	+	..	RF. and chorea recently.	..	1/4
139	21	3 mths	+	+	..	RF. in childhood.	1/8	0
140	21	3½ „	+	+	..	Same case.	0	0
141	51	6 „	+	0	28/100	..	1/16*	0
142	59	1 yr	+	0	72/100	..	..	0
143	22	1½ yrs	+	0	19/100	Early spondylitis; mitral stenosis.	0	0
144	3	1½ „	+	0	..	..	0	1/4
145	25	3 „	+	0	24/100	..	0	..
146	60	5 „	+	0	13/100	..	0	0
147	56	5 „	+	0	60/100	..	0	..
148	39	5 „	+	0	51/100	*B. coli* bacilluria.	0	..
149	60	5 „	+	+	..	..	..	0
150	49	7 „	+	0	Norm.	‡ Gout. Blood uric acid 2·4 mg. per 100 c.cm.	0	0
151	Adult	7 „	+	+	72/100	Iritis.	..	0
152	58	10 „	+	0	..	..	..	1/4
153	42	11 „	+	..	29/100	..	0†	0
154	36	15 „	+	0	31/100	Mitral stenosis.	0	1/4
155	46	26 „	+	..	..	..	0	0
156	Adult	..	+	..	..	..	0	0
157	60	Many yrs	+	0	61/100	..	1/16	1/16
158	..	..	+	..	..	..	1/4	1/16
159	Young adult	..	+	..	..	Recovering.	0	0
160	..	..	+	..	..	..	1/8	1/4
161	..	..	+	..	..	..	0	..
162	..	..	+	..	..	..	1/4	..
163	..	..	+	..	..	..	0	0

* No agglutination with suspension No. 15 (see Table I).
† Agglutination 1 in 8 with suspension No. 15.
Norm. = normal.

In each case studied, the important clinical data at the time when the serum was taken are given in order to indicate any bearing of the clinical stage of the disease on the agglutination reaction. This aspect is stressed in Table III where serum was examined from individual cases at intervals during the clinical course of acute rheumatic fever.

Discussion

Suspensions of particles bearing a close resemblance to elementary bodies of known virus infections have been prepared from a variety of materials from cases of acute rheumatic fever, rheumatoid arthritis, and chorea. Comparison of the morphological characteristics of these suspensions with others prepared by similar technical procedure from sources unrelated to rheumatism call for some discussion. It has already been pointed out that these non-rheumatic suspensions bear a close resemblance to those obtained from true rheumatic sources and to undisputed virus elementary bodies of comparable size. Suspensions prepared from tissues and from any infective pathological exudate show large numbers of these particles which are indistinguishable on morphological grounds from known virus bodies, but contain in addition large numbers of particles of varying sizes and degrees of density. Pericardial, pleural, and joint exudates contain the particles of uniform size and density to a much greater degree than other materials from acute rheumatism and rheumatoid arthritis or from non-rheumatic materials.

Since these particles are not confined to rheumatic infection, agglutination tests have been used to test for their relation to rheumatism. From Table I it appears that the suspensions obtained from pleural, pericardial, and joint exudates are specifically agglutinated, thus lending support to the observation that the preponderance of particles of regular size and density observed in these may be true virus bodies. Suspensions from such sources as blood, urine, cerebrospinal fluid, subcutaneous nodules, and ascitic fluid, contained relatively few of these particles, and were not suitable for agglutination tests. In only one instance was a suspension from synovial membrane from rheumatoid arthritis specifically agglutinated. This is not surprising, since the period between primary infection of the joint and removal of the membrane makes it exceedingly unlikely that large quantities of the infecting agent would still be present. Fibrin from acute pericarditis, on the other hand, yielded suspensions that were specifically agglutinated probably by reason of the exudate present. *The control suspensions (see Table I), which were selected to cover a wide range, were in no case agglutinated by any of the known positive sera.*

When the agglutination results from Tables I, II, III, and IV are studied, it is clear that not only are suitable suspensions from acute rheumatic fever, rheumatoid arthritis, and chorea (C.S.F.) agglutinated by the sera of patients suffering from the particular disease from which the suspension was prepared, but also that considerable cross-agglutination appears within the group of rheumatic diseases. From these results it would seem that these diseases are closely related. While it cannot be said that their ætiology is identical, it is at least probable that they possess some common significant factor which is reflected in serological tests.

The conception of rheumatic fever and rheumatoid arthritis as closely related diseases is supported by other investigators. Dawson and Tyson (1936) support the hypothesis that the two diseases are intimately related, and possibly different manifestations of the same fundamental pathological process, on the evidence of familial relationship, geographic distribution, initiating factors, seasonal incidence, age-incidence, and clinical manifestation in different age-periods, pathological similarity of the subcutaneous nodules and streptococcal immunological findings. Timbrell Fisher (1937) found that the pathological histology of the synovial tissues of uncomplicated forms of the rheumatoid type of arthritis of so-called unknown ætiology and of acute

rheumatism presented a similar and specific picture. From the type of reaction presented a virus ætiology either alone or in conjunction with some other factor was suggested.

Collins (1937), however, in a histological study of the subcutaneous nodules in both these diseases concluded that there was insufficient evidence of resemblance to postulate either a close pathological relationship or a common ætiology of these structures.

It may be argued that the common factor need not be of ætiological significance but may be some non-specific cause such as pyrexia or increased erythrocyte sedimentation-rate. The series of cases examined is sufficiently comprehensive to show that the agglutination titre does not run parallel with either of these factors. Schlesinger, Signy, and Amies observed the fact that increased erythrocyte sedimentation is not responsible for the agglutination. In our series, also, sera from non-rheumatic sources, selected on account of their high sedimentation index, gave completely negative results. Until these suspensions are proven to be infective the possible nature of the reaction must be considered particularly in the light of certain serological observations made in other diseases.

Tillet and Francis (1930), for example, showed that a substance, fraction C, probably a non-nitrogenous sugar, which they isolated from pneumococci and which was chemically distinct from the specific capsular carbohydrate and the somatic nucleoprotein, was precipitated by pneumonia sera in the acute stage of the disease, by the sera of acute rheumatic fever in the active stage with pyrexia, and by sera from acute streptococcal and staphylococcal infections. The course of the temperature and the capacity of the sera to precipitate fraction C ran closely parallel so that in convalescence the reaction was no longer present. Other sera having no relation to pneumococci, streptococci, staphylococci, or acute rheumatic fever were negative, although the temperature was elevated in all cases. Schlesinger, Signy, and Amies considered the possibility of a relationship between the agglutination and streptococcal infections, but were unable to find evidence in its favour, except in one doubtful case with a slightly raised temperature. In our own test and control sera no evidence was found that elevated temperature had any influence on the agglutination reaction. In view of a virus hypothesis for rheumatism the possibility of a reaction between the patient's own serum and exudates was considered, particularly in the light of the observations of Hughes (1933) in yellow fever. Here it was found that a precipitation occurred when the serum of a monkey recently recovered from severe yellow fever was put up with its own serum taken during the period of acute illness. This precipitinogen was not the virus of yellow fever as shown by infectivity tests, but appeared to be associated with a protein of the albumin fraction. Its concentration reflected the severity of the illness, since it disappeared with recovery. The resulting precipitin, which also occurred in the serum of human patients recently recovered from a severe yellow fever infection, was entirely independent of protective antibody resulting from an infection. With this in mind, dilutions of serum from a patient gravely ill with rheumatic fever in the acute stage were set up in hanging drops with his own pleural exudate after it had been centrifugalised for 1 hour at 14,000 rev. per min. As a result of this centrifugalisation a suspension of typical rheumatic bodies had been obtained which was specifically agglutinated by the patient's own serum as well as by other acute rheumatic sera which showed at the same time definite agglutination with other acute rheumatic suspensions. The hanging-drop preparations of serum dilutions and supernatant of the pleural exudate remained perfectly clear when examined microscopically over five successive days. No trace of precipitation was found with other known positive sera and this pleural exudate. It is significant to record, also, that a suspension of washed vaccinia elementary bodies remained unaffected after standing overnight in a pericardial exudate from rheumatic pericarditis, which had been spun for 1 hour at 14,000 rev. per min., and resuspended. These bodies, both before and after remaining in contact with pericardial exudate, gave completely negative results with known positive acute rheumatic fever sera.

The cases of rheumatic disease investigated were chosen to include the three well-known members of the group—rheumatic fever, rheumatoid arthritis, and chorea, with particular reference to agglutination and the bearing which the clinical findings in each case had upon it. For full details Tables II, III, and IV should be studied. The results may conveniently be summarised in the following Table (V),

TABLE V

Summary of Agglutination Tests from Tables II and IV

Type of case from which serum was obtained.		Reference.		Cases.	Agglutination of suspensions from—					
		Table.	Group.		RF.		RA.		Chorea (C.S.F.).	
					+	0	+	0	+	0
Active RF., without carditis or chorea		II	1	4	2	2	1	2	..	..
Active RF., with carditis		II	2	67	31	36	12	7	5	2
a	With subcutaneous nodules	II	2	21	13	8	5	2	2	..
	Without subcutaneous nodules	II	2	44	17	27	7	5	3	2
b	First attack	II	2	28	17	11	8	1	3	..
	Recurrence	II	2	36	13	23	4	6	2	2
c	Recent throat infection	II	2	17	10	7	3	2	2	..
	No known recent throat infection	II	2	46	20	26	9	6	3	2
Inactive RF.		II	4	9	4	5	2	4	2	3
Chorea alone		II	3	8	5	3	1	1	1	..
RA.		IV	..	26	7	14	6	15	..	..
Control sera (see p. 423)		..	..	21	0	21	0	1	0	1

where an analysis of the number of sera in each group and the ratio of positive to negative agglutination and the extent of cross-agglutination is available. The rheumatic fever group is divided into the main clinical subdivisions and the outstanding clinical data for each are indicated along with their effect on agglutination.

The low titres obtained even with the best positive cases may attract notice, but it has to be borne in mind that in most virus diseases so far studied by the serological methods employed in this work, antibody titres never reach the high levels characteristic

of bacterial infections in which the antigen employed is derived from the cultivated organism.

Summary

The main findings of interest may be summarised briefly. Sera from patients suffering from rheumatic fever, chorea, and rheumatoid arthritis agglutinate suspensions from the corresponding disease. Cross-agglutination occurs within the whole group with sufficient regularity to point to an inter-relationship and to hypothecate for rheumatoid arthritis and chorea a possible virus ætiology similar to that of rheumatic fever.

Agglutination of rheumatic fever suspensions by rheumatic fever sera occurs in various types of the disease in the active stage and also when it has become inactive. Stated in general terms, the number of sera giving positive agglutination is about equal to those showing no agglutination. It is difficult to assess the relationship of carditis to the agglutination tests since it is an almost constant manifestation of active rheumatic fever of the acute type, but it is evident that activity of the infection alone does not govern agglutination.

The presence of subcutaneous nodules, which is regarded as an evidence of widespread infection as well as activity, does not run parallel to agglutination, but it is perhaps suggestive that in these cases a considerably larger proportion of sera failed to agglutinate the rheumatic suspensions when nodules were absent than when they were present. A suggestively higher proportion of positive agglutinations occurred with sera of cases suffering a first attack when compared with those in which the disease showed recurrence. This finding may have some significance in the occurrence of remissions.

When the serum of individual cases of rheumatic fever was tested for agglutination with agglutinable rheumatic fever suspensions at intervals throughout several weeks and in some instances several months, it was not possible to correlate the presence or absence of agglutination with any definite phase in the clinical condition. It was realised, however, that before real significance could be attached to correlative investigations of this kind individual cases must be studied over longer periods than has been possible in this investigation.

Until further evidence of the nature of the agglutination reaction in rheumatism is obtained, or the infectivity of the particulate bodies proven, it should be assumed that it is specific for the rheumatic group, and in the absence of definite proof of a bacterial ætiology, as evidence of possible virus infection.

We wish to thank the medical staffs of many hospitals for placing their cases and clinical material at our disposal throughout this investigation. Our thanks are also due to Mr. W. T. Russell, of the department of epidemiology and vital statistics, London School of Hygiene and Tropical Medicine, for statistical advice.

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HYPOSPADIAS

ITS EFFECTS, SYMPTOMS, AND TREATMENT

A REVIEW OF 101 CASES

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THE urethral passage normally opens at the tip of the glans penis, or rather just below it, but in the condition known as hypospadias the opening falls short of the tip of the glans and lies upon the under-surface of the penis or even further back. The complete development of the whole passage of the urethra is made up of two main portions—the part that is formed from the bladder end comprising the major part of the normal urethra, which *has the controlling mechanism of micturition complete;* and the part that may be termed the fovea glandis, which is a pit on the tip of the glans of varying but not considerable depth. By the meeting of the two parts the fully formed urethra is completed. In certain cases of hypospadias the opening of the posterior part of the urethra may be far away from the glans, but in others it may be quite close to the glans and even upon it, though the two portions of the urethra do not become one, as in the normal condition. More than this, the opening of the posterior part of the urethra may lie actually within the fovea glandis; this may be named "concealed hypospadias."

The normal meatus urinarius is rather a complicated structure. It is a vertical slit, and since the passage of the urethra is a horizontal slit a rifling action upon the flow of urine is produced, which aids in the act of micturition. This is well known, but it may not be so well known that two distinct vertical plaques lie one on each side of the normal meatus, somewhat like the appearance of stomata upon a leaf. They doubtless assist in closing the urethra after micturition, and thus prevent an undue formation of drops at the meatus after the act. In any operation for the plastic cure of hypospadias, if this fovea glandis is present it should be preserved and used for the meatus, if this is possible. On the other hand, the opening of the hypospadias may be small and its edges bloodless and thin, in fact almost membranaceous; its appearance is then very different from that of a normal meatus.

CLASSIFICATION

The types of hypospadias in this series of cases may be classified as usual according to the position of the opening. They may be summarised as shown in Fig. 1.

Concealed.—The abnormal opening of the urethra is situated actually in the meatus itself. This has to be opened up in order to reveal the abnormal opening, when it is found that the true opening of the urethra is small, inelastic, and ventral in position. In order to reveal it the meatus must be opened and examined. This condition occurred in 12 per cent. of the total.

Glandular.—Situated upon the glans, but behind it, though only separated by a short distance (21·5 per cent.).

Coronal.—At the level of the corona glandis; what remains of the frænum may be perforated by the opening (12 per cent.).

Post-coronal.—Just behind the corona (20 per cent.).

Corporeal.—Lying somewhere upon the body of the penis in front of the scrotum (3 per cent.).

Peno-scrotal.—At the junction of the penis and the front part of the scrotum, and is rare (1·5 per cent.).

Scrotal.—The opening appears in the scrotum itself and the condition is rare (3 per cent.).

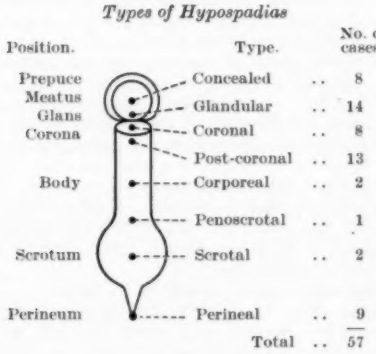
Perineal.—In this condition the opening is situated in the perineum behind the scrotum, or rather the position of the scrotum, which is in two parts either completely, or in a portion of it (13·5 per cent.).

Multiple small openings occurred in 12 per cent. of the total. In no case was the opening at all large; but sometimes it did cause some difficulty in controlling the direction of the stream, and in one case gave rise to a double stream. The accessory opening was affected with gonorrhœa in one case. Once the opening was narrow, and in another case it was quite large and made a wide communication with the second passage.

A very common feature of hypospadias is the well-known and generally recognised hooded prepuce, but there is another that may not be so generally known. There is often a band that unites the edges of the hooded prepuce, such as one that might tie and fix

FIG. 1

Types of Hypospadias



an academic hood. This appears to cause obstruction to the flow of blood, and the prepuce may be not only redundant but œdematous. The treatment necessary for the first four minor varieties that occur in or near the glans penis is very different from that for the major degrees, but before a description is given of the treatment, the disadvantages of the condition may be stated briefly.

DISADVANTAGES OF HYPOSPADIAS

Æsthetic.—The hooded prepuce is quite obvious in all the varieties and especially if it is œdematous.

Deformity.—The curvature of the penis may be very pronounced under normal circumstances, but when erection takes place then the curvature becomes more pronounced, and may prevent the penis from entering the vagina.

The *flow of urine* may be altered from a forward to a downward direction. The clothes are constantly wet not only because of the position of the hole of the urethra but because of the absence of the delicate mechanism for closing the normal meatus. Here it is pertinent to point out the disadvantages of these two latter conditions. Curvature may prevent coitus, the altered direction of the stream of urine leading possibly to a misdirected flow of semen. Thus not only the penis but the semen may fail to enter the vagina. I saw in my practice a girl who had apparently no vagina, but when a dissection was made it was found that the usual opening of the urethra was covered with a strong membrane, which was open only anteriorly and through this micturition was possible. At the same time in Guy's Hospital there was a woman in whom an open operation was necessary in order to allow the birth of a child, and no vagina could be discovered. It seems that it may have been a similar type of case to that of the girl, but it shows that neither entry of the penis nor the immediate introduction of semen is essential for conception. These facts, of course, are well known. There was one case at least of hypospadias in my series in which the father had several children by his wife though the stream of urine was directed downwards. It will be shown later that even the major varieties may not affect sexual relations.

Size of opening.—The smallness of this may be serious. The opening may be only a pinpoint, and in young subjects it may lead to dysuria with great pain during the flow, and even retention of urine. By becoming septic it may give rise to cystitis and orchitis, and in one case there was reason to suspect renal trouble, which may have been septic. In one case a man had passed a stone along the urethra, where it had been arrested in its progress. The surgeon who saw the man at the first had, I think unwisely, removed the stone through an incision over it—i.e., in the urethra—and appeared to have neglected the possibility of a small opening even in a minor degree of hypospadias. Be this as it may, the wound did not heal, and the patient had a urethral fistula for thirteen years. In another case the obstruction and possibility of an ascending infection may have been responsible for the formation of a stone in the bladder.

Prolongation of an attack of gonorrhœa.—It is well known that this predisposes to a stricture, and in three cases at least there was a stricture in the usual position in the urethra, in addition to the small opening of the meatus.

Retention of urine.—A small meatus has been shown to lead to this in young people, but also it may turn the scale in favour of a retention in cases of older people suffering from stricture or enlarged prostate.

Proneness to sepsis is a very real danger as has been shown previously. In connexion with this and the last disability the following case may be quoted.

An elderly man had retention due in the main to an enlarged prostate. I was summoned because there was much difficulty in passing a catheter. The patient showed a fovea glandis that was normal in size and appearance, but he had a hooded prepuce, and a small opening of a hypospadias which lay near the corona glandis. The passage of a catheter through this opening was comparatively easy, and the retention was relieved. An operation for prostatectomy was performed by another surgeon. The wound was long in healing, and I often wonder if sufficient allowance was made for the small opening of the meatus.

Difficulty in "sexing" occurs in the perineal varieties, which has also other great disadvantages. The wetting of the clothes is inevitable unless the patient micturates as a woman does. Also there may be difficulty in coitus, though this is not always so. Thus a man consulted me for syphilis which he had contracted in the usual way in West Africa. He married after a successful operation for the condition of perineal hypospadias. The difficulty of deciding to what sex the patient belongs is greater at birth than later in life. A small penis is very like a large clitoris; the opening of the urethra may be so large as to suggest a vagina, and the scrotum being in two halves may simulate the labia majora. There was no incontinence, however, save in one case and even then it was very doubtful, and may have been of the enuresis type. If there be any doubt about the sex the child should be examined under an anæsthetic, which will reveal the absence of the

uterus. The testes are not necessarily absent, or undescended, and an anæsthetic will assist in their palpation even when they are situated in the abdomen. Usually there should be no reasonable doubt about the sex though at birth there may be necessity for caution in the expression of any views, and this may be very properly delayed.

For what do patients seek advice who are suffering from hypospadias, mild or grave? The following are the main reasons. The friends noticed something wrong. The child had pain, dysuria, or even retention. The condition was quite obviously wrong, or the patient had been rejected for the public services. Often however the patient was not aware that there was anything the matter with him and sought advice for something else, such as a stricture or an enlargement of the prostate, or he noticed that there was difficulty in intercourse. Patients may be of all ages when the condition is discovered.

TREATMENT

In my hands plastic operations designed for the relief of the minor degrees have not led to the success anticipated from the good results experienced in similar operations for the major varieties. Short of a plastic operation, if there are difficulties in micturition—namely, pain, dysuria, and retention—the small opening should be gently dilated, but by no manner of means should it be split. The surrounding parts are so thin and membranaceous that after being cut they do not heal well, and the patient thus may be rendered worse. Gentle dilatation of the opening with an olive-headed or metal instrument, even when only done once, may affect a permanent cure. This was done on a boy aged 12 with excellent results. The treatment may require one or two sittings, but all the cases that have been treated in this way have done well. Another method of dilatation that has been adopted is that by means of a laminaria tent. The patient is instructed to pass urine some time after drinking water. A laminaria tent is then introduced into the opening, and if needed an anæsthetic may be given for this introduction. The tent is allowed to remain in position for nine hours, and after its removal the opening is as a rule widely dilated, without pain. There is no reason against the introduction of a second tent, and similar precautions are taken with this. This treatment is not advocated for children, but for young men it is excellent. While dilatation is proceeding no visitors should be allowed and the patient should be kept quiet.

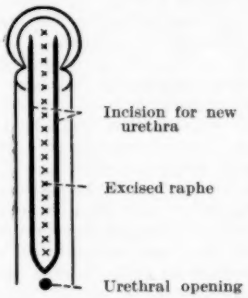


FIG. 2.—Diagram showing position of incisions for excising raphe and for forming new urethra.

In one case a very neat little operation was done for the making of the flow of urine more normal.

The patient had been rejected for the army, and desired an operation. A circular incision was made about 1/16th in. from the edge of the meatus, which was situated near the fovea glandis. A second almost concentric incision was made external to this, and thus a circular strip of tissue between the two incisions could be removed. This was done, and care was taken that the area was wider above than it was below. The edges were then united together. By this means the meatus opened more forward than before the operation, and the result was that the flow of urine was directed forwards, and with a greater force.

For the graver varieties a bigger operation is needed, and I have been bold enough and obstinate enough to do a similar operation through the past twenty-four years on all the patients. It must be confessed that the results, as a rule, were excellent, and most gratifying. This operation was based on two cases that were recorded in 1920 (*Lancet*, 1920, **2**, 790). Since then I have adopted the same methods, subject of course to slight alterations to meet particular emergencies.

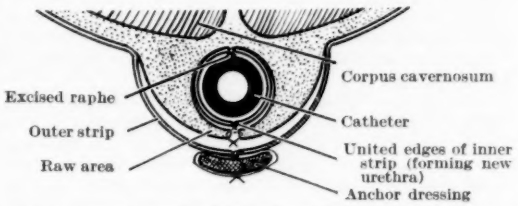


FIG. 3.—Cross-section of penis showing method of forming a new urethra over the catheter.

Before an operation upon adults is carried out the patient should be given potassium bromide gr. 5 every four hours and a light diet. The parts being previously and carefully rendered aseptic, an anæsthetic is administered, and the patient is placed in the lithotomy position with a fair-sized block covered with a clean towel under the buttocks. The dorsum of the prepuce is secured in a Lane's forceps, and put on the stretch. This stretching must be allowed for during the operation. The central raphé of the penis is then deliberately excised, for I find that there is scar tissue in this region, and this is responsible for the deformity of the penis during erection—in some cases even without erection. A linear strip about $\frac{1}{4}$ in. wide is excised from the penis, or the glans if there is a good fovea, to a level just in front of the opening of the hypospadias. The strip of skin is then excised and the edges are sutured with fine catgut. The sutures should not be spared. A No. 5 English gauge or smaller catheter is introduced into the bladder, and secured in position. It must not be so large as to produce tension. Incisions $\frac{1}{2}$ in. apart are then carried from the glans to beyond the opening of the hypospadias on each side (Fig. 2). The meatus if necessary should have been dilated beforehand, but no incision should be so planned as to interfere with it; this is a very important point. The medial edges of each incision are then united with fine catgut over the catheter, care being taken that the deep part of each suture is superficial to the catheter. It may happen that a part of the edge in front is at right angles to the main part; if so any stitch that is inserted must also be at right angles to the general line of the sutures. Anyone who has experience of sewing a kidney knows how important it is that all sutures should be at right angles to the edges of the renal wound, and the same rule applies in these cases. In order to maintain tension at a minimum over the catheter the inner edges may be undermined deeply, but not extensively. Thus a cutaneous tube is formed over the catheter, on both sides of which is a raw area bounded by the outer edges which are then similarly undermined. These raw areas are united with each other by a series of fine catgut sutures inserted Lembert-wise, which should not be spared, for they are very important. The outer edges are then united with salmon gut, but after they have been tied they are not cut until a piece of gauze has been inserted over the first knots (Fig. 3). The long ends of each sutures are then tied over the gauze, and thus an anchor dressing is applied. The sutures are then cut short, care being taken that they do not prick the patient. There should be no tension on any suture. The catheter is left in position, and the patient is taken back to bed.

The treatment after the operation is very similar to what it was before, potassium bromide being given and a light diet ordered. The patient should be kept as quiet as possible, and no visitors should be allowed. The catheter is used for irrigation of the bladder twice a day, and it is removed at the end of two days. Perineal section and opening of the bladder so as to drain the urine behind the site of the wound may be recommended in a few cases, but I am doubtful of its efficacy. The superficial sutures are removed later but bias should be toward their retention rather than their removal. Dermatol (Merck) is used for dusting the gauze, which comes away when the salmon gut sutures are removed. This method of operation has also been performed for the minor degrees of hypospadias.

I must here warn my readers about a certain point. In a large number of cases very inaccurate reports have been made by the clerks and dressers attached to the cases, and these results, therefore, are based perforce only on those cases about which careful notes have been made. Out of the total of 101 cases, 65 are carefully reported, but whenever an operation was performed careful notes were made in most cases so that the Table is accurate.

RESULTS OF THE MAJOR OPERATION

(1) Notes poor, anatomy not stated. Cases, 5: total success 0; partial success 2; failure 3.

(2) Anatomy known. Concealed hypospadias, none done.

Type.	No. of cases.	Total success.	Partial success.	Failure.
Glandular	2	2	—	—
Coronal	3	1	1	1
Post-coronal ..	7	4	2	1
Corporeal	2	2	—	—
Peno-scrotal ..	1	1	—	—
Scrotal	1	—	—	1
Perineal	6	6	—	—
Total ..	22	16	3	3

By "total success" is meant that the patient had a normal passage, through the meatal end of which he passed water. By "partial success" is meant that there was some improvement either in the ease or the direction of the flow of urine. The term "failure" means that the operation failed in its design. There was one death—the failure of the operation done for the scrotal type. The patient was an intensely nervous man who developed suppression after the operation and died from uræmia. There were great difficulties associated with this case, rather of a domestic medical nature.

In conclusion it may be stated that only two-thirds of these cases were properly noted and observed. This may mean that the condition was not noted by the patient, but it also leads to the inevitable conclusion that the students were not very painstaking. If this paper leads to an improvement in this respect then the writer will be fully satisfied.

MUNICIPAL HOSPITAL AT HEREFORD.—On July 30th Queen Mary laid the foundation-stone of the new hospital which is being built by the Herefordshire County Council at Hereford at a cost of between £60,000 and £70,000.

SULPHÆMOGLOBINÆMIA

ITS CAUSE AND PREVENTION, WITH SPECIAL REFERENCE TO TREATMENT WITH SULPHANILAMIDE

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THE condition originally called enterogenous cyanosis, thought to be due to intestinal toxæmia, has been shown to be due to the presence of sulphæmoglobin or methæmoglobin in the blood, and the large majority of cases reported are associated with prolonged or otherwise excessive ingestion of drugs derived from aniline or nitrobenzene, of which the most important are phenacetin (Snapper 1922), acetanilide (Todd 1926), methylacetanilide (Raven 1928), the more recently introduced sulphanilamide (Colebrook and Kenny 1936, Discombe 1937, Kane 1937, Paton and Eaton 1937), and nitrobenzene itself, the last usually being incriminated in cases of shoe-dye poisoning (Levin 1927). There are, however, some cases of undoubted true enterogenous cyanosis not associated with drugs (van den Bergh and Engelkes 1922, Parsons 1924).

The mechanism by which methæmoglobin is produced in these cases is not yet understood, but the process of formation of sulphæmoglobin is quite clear. Snapper (1922) first showed that phenacetin administered to dogs produced methæmoglobinæmia, but if precipitated sulphur were given simultaneously a sulphæmoglobinæmia developed instead; he was led to this experiment by the observation that two patients with sulphæmoglobinæmia had received phenacetin continuously for about a year, and ceased to be cyanosed after this drug was forbidden, though the cyanosis rapidly returned when more phenacetin was given. This work was continued by van den Bergh and Wieringa (1925), who showed that hydrogen sulphide could react with hæmoglobin only in presence of oxygen (though minute traces were sufficient), and that this combination was accelerated, or catalysed, by the presence of certain substances, all of which were simple derivatives of aniline or hydrazine.

The mechanism by which sulphæmoglobin is formed in vivo is thus demonstrated. Hydrogen sulphide is constantly absorbed from the large gut, being formed therein by the action of bacteria on food residues, or as a result of the administration of elementary sulphur, which is known to be absorbed partly as sulphide. This absorbed hydrogen sulphide is, under normal conditions, partly destroyed by the plasma, and partly excreted by the lungs (Haggard 1921). If a grossly excessive amount of hydrogen sulphide is formed, or if a normal amount of hydrogen sulphide is formed when a catalyst for the combination of hæmoglobin with hydrogen sulphide is present in the blood, some of the sulphide will combine with the hæmoglobin in the erythrocyte; and since this cell, which has a life of several weeks, is not lysed, in course of time a detectable sulphæmoglobinæmia will develop. The time which will elapse before sulphæmoglobin is detected will depend, of course, on the amount of hydrogen sulphide absorbed from the gut, on the nature and quantity of the catalyst administered, and on the delicacy of the technique available for the detection of sulphæmoglobin.

That this reasoning holds for the sulphæmoglobinæmia which follows sulphanilamide treatment is shown by the following experiments.

1. *Catalysis by sulphanilamide of the reaction between hydrogen sulphide and hæmoglobin.*—This has been demonstrated by mixing the reactants diluted with a phosphate buffer solution, diluted in one case with water, in the other with a saturated solution of sulphanilamide. Thus 8 c.cm. of a 9·078 per cent. solution of potassium dihydrogen phosphate and 2 c.cm. of a 11·876 per cent. solution of disodium hydrogen phosphate in water were diluted to 100 c.cm. with water. A second solution was made by diluting the same phosphate mixture to 100 c.cm. with a saturated solution of sulphanilamide. The sulphanilamide buffer solution was allowed to settle till clear, and the supernatant fluid used. No difference in *p*H could be detected between the tubes (*p*H 6·3).

In a 6 in. by 1 in. test-tube were placed 20 c.cm. buffer solution, 0·5 c.cm. of laked blood, and 0·5 c.cm. of a very dilute solution of ammonium sulphide; in a similar tube were placed equal volumes of sulphanilamide buffer, blood, and ammonium sulphide. The two tubes were examined spectroscopically, both along the long axis (2 in. column of fluid) and transversely (1 in. column), and the time which elapsed before the α-band of sulphæmoglobin could be seen was recorded.

In one experiment it was found that in the control tube the band could be just seen after 10 minutes when looking down the long axis of the tube, and was definite only after 20 minutes; viewed transversely the corresponding times were 29 and 55 minutes. When sulphanilamide was present these times were reduced to 3½, 7, 11, and 21 minutes respectively.

The results of the first experiments confirm the hypothesis of Snapper and van den Bergh, and are not in agreement with a recent publication on the subject. To demonstrate the catalysis it is necessary to use much higher concentrations of catalyst than are possible in vivo, and to use only traces of sulphide to keep the reaction from too rapid completion.

2. *Production of sulphæmoglobinæmia in a volunteer.*—The subject, one of us (G. D.), was given the drugs investigated for periods of three days, and intervals of a week or more were allowed to elapse between tests. He was given first 3 grammes sulphanilamide daily, then 12 grains of calx sulphurata daily, and then both together, with no unusual effects. Later he was given 2 g. sulphur daily for three days, and no sulphæmoglobinæmia could be detected; but when he took 2 g. sulphanilamide and 1·2 g. sulphur during one day, sulphæmoglobin could be detected in his blood the following morning.

It is highly probable that all drugs containing the group $C_6H_5N<$ are capable of causing methæmoglobinæmia and of facilitating the production of sulphæmoglobin. If any new drug containing this group is administered in large doses such complications should be anticipated. In some cases the catalytic action on the hæmoglobin-sulphide reaction may be demonstrated in vitro, in other cases this may prove difficult or impossible—for example, when the drug is almost insoluble in water. For such insoluble drugs trial on suitable animals will be necessary.

ACTION OF MAGNESIUM SULPHATE

The action of magnesium sulphate in accelerating the production of sulphæmoglobinæmia is less easy to understand. Dr. George Graham has pointed out to us that this substance appears to increase the production of hydrogen sulphide in the gut, so far as may be judged by observation; excessive quantities of hydrogen sulphide may be produced by other purges, but the effect is more marked and constant with saline purges than with others.

For this reason and because of the great absorption of energy required to effect the reduction of sulphates to sulphides, we think it improbable that the hydrogen sulphide formed after administration of sulphates is derived by reduction of the sulphate. An alternative explanation is possible, and in our opinion more probable. In the gut magnesium sulphate is dissociated into magnesium and sulphate ions; the magnesium usually forms some insoluble compound, while the sulphate ion remains in solution, and only traces are absorbed. The presence of this unabsorbed dissolved material increases the osmotic pressure of the gut contents, so that water will pass from the body fluids into the lumen of the gut (cf. Witts 1937). Absorption of fluid from the colon will be correspondingly reduced, and the more liquid contents of the colon will form an admirable medium for the growth of bacteria; further, by the action of purges the absorption of food is decreased, and more passes to the colon unabsorbed. Since many bacteria normally present in the colon split cystine to form hydrogen sulphide, an increased production of hydrogen sulphide may reasonably be expected.

Any treatment which helps the formation of a liquid stool may be expected to accelerate the formation of sulphæmoglobinæmia. Liquid paraffin, since it acts as a mechanical lubricant, is the only laxative which can be relied on to prevent the formation of scybala without the risk of accelerating the appearance of sulphæmoglobinæmia. If liquid paraffin is insufficient, or if constipation is severe, it may be necessary to use enemata, the residues from which are rapidly absorbed, leaving the gut clean and dry.

TREATMENT TO PREVENT SULPHÆMOGLOBINÆMIA

We have therefore designed a régime for patients who are treated with sulphanilamide, in the hope of preventing or at least delaying the onset of sulphæmoglobinæmia. We consider this justifiable since it is impossible to decide, before treatment is started, how long it will be necessary to continue with this drug; while extreme degrees of sulphæmoglobinæmia *must* be avoided since they may lead to dyspnœa relieved only by blood transfusion.[1] Abstention from purges is not in our experience enough to prevent the development of sulphæmoglobinæmia.

Our aim has been to maintain the colon as free as possible from food residues and from water, so that bacterial decomposition should be reduced to a minimum. To this end the patient is placed on a low-residue diet, of calorific value sufficient to provide for the increased metabolism due to the pyrexia; only the minimum number of eggs (one or two daily) are given, since these contain, for the same weight of protein, two or three times as much sulphur as other foods. Miss M. Abrahams, the hospital dietitian, has informed us that it is not difficult to produce a low-residue diet containing as much as 3500 calories (typhoid-convalescent diet); since a 14 st. man, 6 ft. 1 in. tall, has a basal requirement of only 1980 calories daily, this should suffice even if his average temperature rose to 104° (we have not used diets as large as this). Unless diarrhœa is present, 30–45 c.cm. liquid paraffin is given daily, and all other aperients are forbidden. If constipation develops, enemata are given, while if the patient has recently received magnesium sulphate the colon should be thoroughly washed out.

One further precaution is desirable. Phenacetin is a most useful analgesic drug, but is itself capable of facilitating the formation of sulph- and methæmoglobin. For this reason its use with patients who are

[1] In contrast, methaemoglobinaemia, however intense (we have seen one case showing 60 % (Haldane)), is of little importance to the patient, since it disappears within 24 hours of the cessation of treatment.

receiving sulphanilamide should if possible be avoided; though if the diet is satisfactory and no laxatives are used it seems fairly safe. This may be too rigorous a precaution, but is reasonable since sulphanilamide can produce agranulocytosis (Nettle 1937, Young 1937), and little is known of any synergistic actions in this group. In most of the cases recorded here all coal-tar drugs have been avoided, and if given the total dose is specified.

CASE REPORTS

Cases 1–9 show that this treatment is reasonably, though not completely, successful. Case 10 shows sulphæmoglobinæmia following purgation with calomel; Case 11 shows a hitherto undescribed toxic reaction; Cases 13–15 received benzyl-sulphanilamide (Proseptasine) and Soluseptasine; it is interesting to note that these substances also can induce sulphæmoglobinæmia; Cases 12, 16, and 17 are discussed in detail separately, since they illustrate points of special interest.

CASE 1.—A. B. Aged 16. Ulcerative colitis. Received 60 g. sulphanilamide in 20 days; low-residue diet, no laxatives; passage of fæces through colon abnormally rapid. No abnormal pigment was detected in the patient's blood.

CASE 2.—Miss C. D. Aged 10. Acute nephritis. Received 15 g. in 12 days. Diet with very little residue, almost free from protein; occasional aperient (cascara). No abnormal pigments found in the patient's blood.

CASE 3.—Miss E. F. Aged 35. Erysipelas, osteomyelitis right tibia. Received 48 g. in 12 days. On admission received a single dose of magnesium sulphate; three days later transferred to a low-residue diet, with liquid paraffin, and sulphanilamide treatment started. Methæmoglobin was present on the 5th, 10th, and 12th days of treatment, slight cyanosis being observed on the last occasion. No sulphæmoglobin could be detected.

CASE 4.—Mrs. G. H. Aged 66. Cellulitis right foot and leg; ulcer on plantar aspect of first metatarsophalangeal joint; diabetes mellitus. Received 15 g. in 5 days; low-residue diet, liquid paraffin. No abnormal pigments found in her blood. (Several other patients receiving small doses have been seen; none have developed sulphæmoglobinæmia.)

CASE 5.—Miss I. J. Aged 17. Axillary abscess; drainage; septicæmia, hæmolytic streptococci grown in blood culture. Received a total of 68 g. in 15 days. On the 13th day of treatment was markedly cyanosed, with methæmoglobinæmia (53 g.); on the 16th day, 12 hours after the last dose of sulphanilamide, the cyanosis had disappeared, though a slight methæmoglobinæmia remained; on neither occasion could sulphæmoglobin be detected.

CASE 6.—K. L. Meningococcal meningitis (Type I meningococcus). In the 48 hours following admission received 152 c.cm. meningococcal antitoxin, and 80 c.cm. Prontosil soluble. In the next 11 days received 36 g. sulphanilamide, and 7·3 g. phenacetin. Examination on the 14th day after admission showed no abnormal pigments in his blood. His diet contained little residue; he received four doses of the pulvis ipecacuanha co. (B.P.C.) during the first 4 days in hospital. No purgatives were given.

CASE 7.—M. N. Aged 56. Tuberculous abscess second right rib, involving sternoclavicular joint; miliary tuberculosis; hæmolytic streptococcal infection of biopsy wound; streptococcal septicæmia. On May 10th the abscess was opened and the walls scraped. On May 2nd and 18th hæmolytic streptococci were grown from his throat, and on June 1st from the wound. Two courses of sulphanilamide, from May 14th to 24th and from June 4th to 19th, were given, total 96 g. During the courses a low-residue diet and liquid paraffin were given, but before and between these courses frequent doses of magnesium sulphate were given. On examination on June 24th, no abnormal pigment could be detected in the blood; although this was the fifth day after cessation of treatment, this is sufficient to show that only traces of sulphæmoglobin could have been present during treatment.

CASE 8.—Mrs. O. P. Aged 34. *B. coli* infection of urinary tract. This patient was placed on a low-residue diet for 3 days before sulphanilamide was given. After 6 g. had been given she appeared cyanosed, and a faint band of sulphæmoglobin, insufficient to cause cyanosis, was observed in her blood. Treatment was suspended and resumed after 10 days. After 10 days' treatment (30 g.) and on the 18th day (57 g.) methæmoglobin, but no sulphæmoglobin, could be detected in her blood.

CASE 9.—Mrs. Q. R. Aged 46. Deep X ray treatment of an ulcerating post-cricoid carcinoma; streptococcal septicæmia. In 11 days 35 g. sulphanilamide was given; on the 13th day from the start of this treatment a definite, though weak, band of sulphæmoglobin could be seen in her blood, though she had received a low-residue diet and liquid paraffin. Cyanosis was not observed.

CASE 10.—Miss S. T. Aged 17. Post-partum pyrexia. On March 11th received 3 grains of calomel; on this and the next two days received a total of 3·9 grammes sulphanilamide orally and 60 c.cm. prontosil soluble intramuscularly. On the 13th she was deeply cyanosed with marked sulphæmoglobinæmia. She received no sulphates.

CASE 11.—Miss U. V. Aged 15. Erysipelas. After 1 g. sulphanilamide her temperature fell abruptly to normal; during the next 32 hours she received 6 g. sulphanilamide. After 5 g. had been given she was observed to be very drowsy; after the last dose her temperature fell to 97°; pulse 90, weak; respirations 25, shallow; she appeared collapsed, and was heavily cyanosed. During the next few hours she rapidly recovered, and eight hours later appeared almost normal, though methæmoglobin could be demonstrated in her blood.

This appears to be a true case of sulphanilamide idiosyncrasy, as opposed to an ordinary met- or sulphæmoglobinæmia.

CASE 12.—Miss C. W. Aged 48. Drainage of paranasal sinuses; erysipelas of face. Admitted June 14th, operation on 15th. Between June 16th and 22nd received 7·6 g. phenacetin, with frequent doses of magnesium sulphate. On June 21st she received two 30 c.cm. doses of mist. sennæ co. (B.P.C.) and on the 22nd one dose. No stool was passed on the 21st or 23rd and only one on the 22nd and 24th. On the 23rd she was placed on a low-residue diet with liquid paraffin, and at once given sulphanilamide, 3 g. daily. On the 25th she was observed to be cyanosed, with marked sulphæmoglobinæmia, after only 7 g. had been given.

It seems probable that in this case the partly successful attempts at purgation on the 21st and 22nd had filled the colon with moist food residues, so that sulphæmoglobinæmia might have been anticipated. In such cases it is probably essential to give enemata, or better, a thorough colonic lavage, before starting sulphanilamide.

CASE 13.—Miss Y. Z. Aged 42. *B. coli* infection of urinary tract. Diet, vegetable and fruit purées; no laxatives or drugs other than benzyl-sulphanilamide (proseptasine) and soluseptasine. Between June 12th and 17th received 35 g. proseptasine orally and 35 c.cm. soluseptasine intramuscularly. On the 17th a weak band of sulphæmoglobin could be detected in the patient's blood.

CASE 14.—Miss Z. A. Aged 49. Peptic ulcer; *B. coli* infection of urinary tract. Diet, vegetable and fruit purées; received in 5 days 28 g. benzyl-sulphanilamide and 35 c.cm. soluseptasine; during the same period received also ferric ammonium citrate 90 grains and ammonium carbonate 3 grains daily. On the fifth day a faint band of sulphæmoglobin could be seen in this patient's blood.

Neither Case 13 nor Case 14 received a low-residue diet, though the only laxative permitted was liquid paraffin; since one patient had a hæmoglobin of only 28 per cent. Haldane, the occurrence of sulphæmoglobinæmia was of importance.

CASE 15.—Y. B. Aged 30. Septic endocarditis (*Streptococcus salivarius*). In 23 days received 90 g. benzylsulphanilamide orally and 110 c.cm. soluseptasine intramuscularly, and in the next 9 days 36 g. sulphanilamide orally. Low-residue diet, liquid paraffin. No abnormal pigments could be detected in his blood either on the 15th, the 23rd, or the 32nd day of treatment.

USE OF OTHER DRUGS

We have mentioned above that the use of coal-tar drugs should be avoided. The uncritical use of any analgesic or hypnotic drug can endanger life, and when drugs such as sulphanilamide are used the clinical picture may become so complicated that recourse to the laboratory is essential. Such a case may be of interest.

CASE 16.—Mrs. X. C. Aged 26. Septic abortion. This patient was admitted from a nursing-home with a diagnosis of "prontosil poisoning." She was deeply cyanosed, though the cyanosis was not of the peculiar leaden hue caused by sulphæmoglobin, very weak, almost comatose, though she could be roused to answer questions, and smelt strongly of paraldehyde. Temperature 98·4°, respirations 25, pulse-rate 80. A moderately strong band of sulphæmoglobin could be demonstrated in her blood, but the concentration of this pigment was only 2·9 g. per 100 c.cm. (method of Bloem, 1933), corresponding to 21 per cent. Haldane; while the oxygen-combining power was 9·9 c.cm. per 100 c.cm. blood, or 53·5 per cent. Haldane. For this reason it was concluded that the cyanosis was not a direct result of the sulphanilamide treatment, but was due mainly to the over-enthusiastic use of paraldehyde and possibly other drugs. The treatment was simple—rest, and plenty of fluids by mouth. When seen 36 hours later the cyanosis had completely disappeared, the patient was cheerful and appeared anxious to leave as soon as possible; she was discharged after 10 days.

IMPORTANCE OF SPECTROSCOPIC EXAMINATION OF THE BLOOD

The importance of spectroscopic examination of the blood of patients who develop cyanosis when treated with sulphanilamide cannot be exaggerated. Cyanosis following sulphanilamide is not invariably due to met- or sulphæmoglobinæmia; methæmoglobin cyanosis often diminishes in intensity when the dose of drug is increased. We have seen patients develop cyanosis and sulphæmoglobinæmia simultaneously, yet the concentration of sulphæmoglobin remained far too low to account for the cyanosis (Cases 16 and 17). In such cases spectroscopic examination of the blood, followed by an approximate estimate of the concentration of sulphæmoglobin by a simple method such as that of Bloem, may be of great value to the clinician. It must be remembered that it is possible to detect sulphæmoglobin in blood when its concentration becomes greater than that corresponding to 4 per cent. hæmoglobin (Haldane). Cyanosis becomes notable when about 30 per cent. hæmoglobin has been converted. The spectroscopic test used on all these patients is therefore some seven times more sensitive than clinical examination.

CASE 17.—Miss W. D. Aged 26. Pyrexia following left antrostomy. In 3 days received 9 g. sulphanilamide; in the previous 15 days had received 13 g. phenacetin; during these periods occasional doses of magnesium sulphate were given. On the third day of sulphanilamide treatment a very slight cyanosis was observed; the patient's blood contained a small quantity of sulphæmoglobin, insufficient to account for any cyanosis. On physical examination evidence of pneumonia was found.

SUMMARY

1. The intracorpuscular sulphæmoglobinæmia associated with the administration of drugs derived from aniline, results from the combination of hæmoglobin with the hydrogen sulphide absorbed from the intestinal tract; this reaction is catalysed by the drug circulating in the blood.

2. The normal absorption of protein digestion products in the small intestine is diminished by purgation, causing increased putrefaction in the colon, and a production of hydrogen sulphide much in excess of normal. Saline cathartics are most active in this process because their osmotic action maintains the contents of the colon in a semi-fluid state, thus accelerating putrefaction.

3. The development of sulphæmoglobinæmia can be prevented or considerably delayed by keeping the colon free from food residues by (1) cleansing the colon with enemata before treatment is started, if purges have previously been given; (2) giving the patient a low-residue diet, of adequate calorie value, containing few eggs; (3) giving large, regular doses of liquid paraffin.

4. In treatment with sulphanilamide, it is important to examine spectroscopically the blood of all patients who develop cyanosis; for occasionally the cyanosis is due not to the presence of abnormal pigments in the blood but to the development of some other organic disease, such as pneumonia.

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FATAL HÆMATEMESIS AND MELÆNA

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THE widely differing mortality-rates from gross hæmatemesis and melæna given by various authors have been tabulated by Babey and Hurst (1936). The figures vary from 1 per cent. (Meulengracht 1935) to 25 per cent. (Chiesman 1932), and there can be little doubt that the greatest part of this variation is due to the differences of opinion as to what degree of bleeding constitutes gross hæmatemesis. It is evident that when all cases of bleeding are taken into account the death-rate is low; but Chiesman, Aitken (1934), and Lloyd Davies and Nevin (1934) have shown that the mortality is very high if only severe cases are considered. In connexion with this last group, in

which medical treatment is obviously unsatisfactory, the question of surgical operation as a means of arresting the hæmorrhage has been raised and has given rise to much argument. The careful study of large numbers of case records is of interest in prognosis, but since almost the only indication for urgent operation in these cases is the presence of a chronic ulcer (Gordon-Taylor 1935) the cause of the hæmorrhage must be known. Lloyd Davies and Nevin did not divide their cases into ætiological groups because even on discharge the exact cause was not proved in a number of them. The careful studies of Hellier (1934) and Shaw (1933) showed that in these two series between 20 per cent. and 40 per cent. were of doubtful origin. Hellier discusses the mortality in patients with proved or probable ulcers, but Hinton (1931a and b) has pointed out that in his experience the patients that died were those with a short or negative gastric history. Any discussion with regard to treatment without first establishing a diagnosis or at least being aware of the possible causes of the bleeding must lead to erroneous conclusions. Too little study has been made of the pathological findings in those fatal cases in which death results from exsanguination and in which there is no reason to suspect on clinical examination that the bleeding has been due to malignant disease or to extra-gastric conditions. It is important in such an investigation to take into account the clinical findings since, if pathology alone is considered, many diseases unsuitable for immediate operation are introduced.

MATERIAL EXAMINED

This paper is based on the clinical and pathological features of a series of 48 patients who died of bleeding from the gastro-intestinal tract in the Western Infirmary of Glasgow, during the years 1925–35, and on whom a post-mortem examination was made. Those cases having severe hæmorrhage but dying of complications such as peritonitis and pneumonia were excluded and also those in whom clinical examination had discovered the presence of malignant disease, hæmorrhagic disorder of the blood, cirrhosis of the liver, or other extra-gastric disease which would have caused the bleeding.

FATAL HÆMORRHAGE FROM PEPTIC ULCERATION

Forty died of bleeding from peptic ulceration; of these, 28 were males and 12 females. In 23 cases the ulcer was duodenal in origin, in 16 gastric, and in 1 it was situated at the stoma of a gastro-enterostomy. Chronic peptic ulcer was found in 26 cases, and in 11 of these the ulcer was adherent to the pancreas. Acute ulcer was the cause in 14. In 32 patients the ulcer was single, but in 8 there was evidence of multiple ulcers either active or healed.

FROM OTHER CAUSES

Other conditions were responsible for 8 deaths. In only one instance was bleeding from carcinoma fatal in the absence of other signs of malignant disease. Two patients had cirrhosis of the liver without appreciable ascites or hepatic enlargement, and 2 had multiple superficial erosions of the stomach. The only lesions found in 2 cases were diffuse hæmorrhages of unknown origin in the gastric mucosa. One patient had an ulcer of the œsophagus situated just below the tracheal bifurcation and eroding the thoracic aorta. This was probably traumatic but no foreign body was discovered.

CLINICAL CONSIDERATIONS

The above are the post-mortem findings. From the clinical standpoint these 48 cases can be conveniently divided into two groups according to the duration of the complaint of pain, but in so doing 4 of them will be excluded, 2 who died of bleeding occurring within forty-eight hours of an operation for another condition and 2 who were in addition suffering from other diseases.

PAIN OF LONG DURATION PRECEDING HÆMORRHAGE

GROUP I.—Twenty-seven complained of gastric pain for more than one month before the onset of the bleeding, and of these 20 had chronic peptic ulcer. In the remaining 7 cases there were 6 of acute ulcer and 1 of cirrhosis of the liver. The 6 persons who bled from acute ulcers despite long complaint of pain are of especial interest. Here the shortest history was two years and the longest twenty years, and in 5 there were signs of more than one ulcer, either active or healed.

NO PAIN, OR PAIN OF SHORT DURATION

GROUP II.—In 17 patients there was either no pain at any time (14 cases) or pain of less than one month's duration (3 cases). In 8 of these acute ulcer was present; in 4 the cause was chronic ulcer. Idiopathic submucous hæmorrhages were found in 2, gastric carcinoma in 1, cirrhosis of the liver in 1, and œsophageal ulcer in 1.

SUMMARY AND CONCLUSIONS

1. Forty-eight patients dying of hæmatemesis or melæna in a period of eleven years are considered. In none of these patients was there any clinical evidence of malignant disease or of extra-gastric lesions which might have caused the hæmorrhage. A post-mortem examination was made in every case. In 26 a chronic peptic ulcer was found; in 11 of these the ulcer was adherent to the pancreas and in 3 the source of the hæmorrhage could not be found. In 14 cases acute peptic ulcer was present and in 8 the bleeding was due either to extra-gastric causes or to lesions other than peptic ulcer.

2. Forty-four of the cases were divided into two groups according to the duration of complaint of pain, the remainder being excluded for reasons given in the text. Twenty-seven cases complained of pain for more than a month before the onset of the bleeding; of these, 20 had chronic peptic ulcer, 6 acute ulcer, and 1 had cirrhosis of the liver. Taking the presence of a chronic ulcer as the primary indication for surgical intervention 70 per cent. were suitable for operation.

Seventeen cases either made no complaint of pain or complained of pain for less than one month. In this group 4 had chronic peptic ulcer, 8 had acute ulcer, and the remainder had lesions other than peptic ulcer. On the same criterion as above there were primary indications for surgery in 24 per cent. of this group.

3. These findings demonstrate the importance of taking into account the duration of pain in the diagnosis of the cause of hæmatemesis. Of these cases who complained of pain for more than one month approximately 3 out of 4 were found to be due to chronic peptic ulcer; when the duration of pain was less than this 1 out of 4 had chronic ulcer. Since only fatal cases are considered in this paper it cannot be maintained that these figures represent the true incidence of chronic peptic ulcer in all series of cases of hæmatemesis. They only indicate the probable findings in cases of the most severe type.

4. If surgery is to be considered as a means of treatment of hæmatemesis and if the presence of a chronic ulcer is essential to success, only the first

group should be subjected to operation. If this selection is made the chances of finding a chronic ulcer are increased and the risk of an unnecessary operation diminished. It must be realised that by selecting cases in this way operation will be denied to the relatively small number of patients with chronic peptic ulcer who have a fatal hæmorrhage without any history of gastric pain. Moreover, whatever the method of selection of cases adopted, great technical difficulties may be encountered during a direct attack on the bleeding point on account of the frequency with which the pancreas is involved.

5. The greatest caution should be observed in assessing the value of any form of treatment of hæmatemesis or melæna. The clinical features of gross gastro-intestinal bleeding with a varying history of dyspepsia may be produced by many diseases. The ætiology and prognosis of each disease may be different; the symptoms alone are similar.

This work was done during the tenure of a Hall fellowship in the department of medicine first under Prof. T. K. Monro and later under Prof. J. W. McNee. My thanks are due to them and also to Prof J. Shaw Dunn for advice and assistance in writing this paper.

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THEOPHYLLINE-ETHYLENEDIAMINE IN CHEYNE-STOKES RESPIRATION

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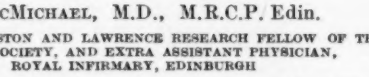
Theophylline-ethylenediamine is a combination of one molecule of theophylline with ethylenediamine.



Ethylenediamine Theophylline

It was first introduced by Grüter (1910) as the result of a search for a water-soluble theophylline preparation for injection. Theophylline itself is very insoluble, and even the double salt of theophylline with sodium acetate is only soluble in 25 parts of water. Theophylline-ethylenediamine however is quite soluble and easily forms a 40 per cent. solution (Grüter 1936). The ethylenediamine compound was used at first because it was non-toxic, but it was soon found that the compound had pharmacological properties not found in other forms of theophylline.

Theophylline-ethylenediamine is suitably supplied in ampoules and tablets under the trade name of Euphyllin, and it is this preparation which we have used throughout this investigation.

ACTION IN CHEYNE-STOKES RESPIRATION

It is now ten years since Vogl (1927) described the use of euphyllin as a means of abolishing Cheyne-Stokes breathing and the accompanying subjective discomfort. It is surprising, therefore, to find that, apart from a paper by Smith and others (1935) describing its influence on paroxysmal dyspnœa, little mention has been made in English of this effect of the drug. Furthermore, its mode of action in Cheyne-Stokes breathing is still in some doubt, and the elucidation of this problem is our main object. Vogl (1932), summarising five years' experience with euphyllin in Cheyne-Stokes breathing, states that it never fails to restore the respiration to a normal type. The action is most pronounced in cases of cardiac insufficiency, but is sometimes transient, especially when the periodic respiration results from head injuries or intracranial hæmorrhage.

The following cases will illustrate the action of theophylline-ethylenediamine. In our description the terms "Cheyne-Stokes" breathing and "periodic" breathing may be regarded as synonymous, although we use the latter term particularly to include regular periodic waxing and waning of respiration without the true apnœic pauses emphasised in the original descriptions of Cheyne and Stokes.

CASE 1. *Syphilitic aortitis and atheroma.*—A retired ship's fireman, aged 68, complaining of periodic breathlessness, and giving a history of precordial pain a month previously. There was no œdema or general venous congestion, but a good deal of bronchitis and pulmonary congestion. The heart was hypertrophied and a double aortic murmur was audible. The Wassermann reaction was strongly positive, and radiography revealed diffuse dilatation of the aortic arch with calcification. Electrocardiograms showed evidence of recent coronary thrombosis. Cheyne-Stokes breathing was pronounced, but became less obvious after rest in bed for a few weeks when the bronchitis and pulmonary congestion had subsided.

On May 31st, 1937, a single intravenous injection of 0·36 gramme euphyllin abolished completely the Cheyne-Stokes respiration during the course of a slow injection (Fig. 1). On subsequent occasions the injection of theobromine sodium acetate (0·6 g.) and of theophylline sodium acetate (0·6 g.) intravenously failed to abolish the periodic respiration. When the latter injection was followed by 0·1 g. ethylenediamine intravenously the Cheyne-Stokes respiration disappeared (Fig. 2). On June 18th the administration of 0·5 g. euphyllin by mouth abolished periodic breathing in about ten minutes.

In this patient the effect of euphyllin was maintained over many hours and breathing was often found to be normal in type up to 16 hours after a single dose of 0·48 g. Oral administration was also quite successful.

CASE 2. *Hypertensive heart failure.*—An engineman, aged 53, complaining of breathlessness on exertion. The blood pressure was 170/100, and he presented the usual features of severe heart failure with congestion—i.e., œdema of the legs and back, ascites, enlargement of the liver, pulmonary congestion, and œdema. The patient failed to show any maintained improvement with a succession of therapeutic measures—including digitalis, salyrgan and other diuretics, salt-free diet, and Southey's tubes—and gradually the orthopnœa became more conspicuous and was accompanied by Cheyne-Stokes respiration. Sleep was definitely disturbed by the periodic hyperpnœa, the onset of deep breaths waking him up as he was dosing off to sleep.

On June 8th, 1937, 0·36 g. euphyllin was administered intravenously and a stethograph record showed the abolition of Cheyne-Stokes respiration as the injection proceeded (Fig. 3). This injection was given in the afternoon and that night the patient got to sleep with ease, having previously required sedatives. On June 11th the injection of 0·16 g. ethylenediamine intravenously was sufficient to abolish the apnœic phases, but periodic increases and decreases of respiration still persisted. The subsequent injection of 0·6 g. theophylline completed the restoration of the respiratory rhythm to normal.

On June 14th theophylline 0·6 g. intravenously alone was without effect and only transient abolition of the Cheyne-Stokes breathing was achieved by 0·16 g. ethylenediamine given a few minutes later. On the 15th, 0·48 g. euphyllin intravenously abolished the Cheyne-Stokes respiration completely for two hours.

This series of observations is of interest in that it seems to show that a single injection of the compound theophylline-ethylenediamine may be more effective than its two components given separately in succession. The action of euphyllin on this patient was not so prolonged as in Case 1. After the final injection, Cheyne-Stokes breathing had returned in two hours.

CASE 3. *Chronic bronchitis and hypertensive heart failure.*—An unemployed miner aged 53. Cough, headaches, and breathlessness for five years. For six months he has had attacks of breathlessness which come on as he is falling off to sleep. These waken him and he fights for breath till the attack passes off. There was œdema of the legs; blood pressure 170/110; heart enlarged; no murmurs; rhonchi and crepitations all over the lungs, the latter most marked at the bases; blood-urea 32 mg. per 100 c.cm.

On June 22nd Cheyne-Stokes breathing was pronounced. It was abolished by 0·60 g. euphyllin intravenously, but returned ten minutes after the injection. The action in this case was transient and the patient was not aware of any subjective improvement.

CASE 4. *Rheumatic heart disease*—A teacher aged 49. History of severe rheumatic fever when aged 11 but, in spite of known cardiac damage, he was capable of considerable exertion including Alpine climbing. For eight years he has been incapable of such severe exercise, and has become increasingly breathless. Five months before admission to hospital he had influenza and since then he has been orthopnœic. The patient showed slight œdema of the ankles, enlargement of the liver, a tinge of jaundice, and engorgement of the veins of the neck up to the angle of the jaw. Blood pressure was 128/60. The heart was grossly enlarged, with systolic and diastolic murmurs at the aortic and mitral areas. The lungs showed œdema at the extreme bases. The patient had pronounced periodic waxing and waning of respiration; he often had attacks of severe breathlessness, particularly at night, which made sleep impossible without morphine.

On June 8th an intravenous injection of 0·48 g. euphyllin was given, resulting in the abolition of periodic respiration (Fig. 4). At the same time the patient stated that he could see better, that his mind became clear, and that his breathing became easier and perfectly steady. In his own words "the difference in breathing was almost unbelievable." That night he had a long undisturbed sleep without a sedative.

On June 10th a respiratory record was taken to show the effect of the two components of euphyllin. Following the injection of 0·1 g. ethylenediamine the respirations suddenly became very deep and rapid with much subjective distress and anxiety. This condition was regarded by the patient as similar to the nocturnal attacks of dyspnœa which wake him up so frequently. After about two minutes the hyperpnœa subsided, but there was no apnœic pause, the respiration continuing in a steady regular fashion, with complete disappearance of periodicity. A few minutes later 0·6 g. theophylline was given intravenously, with no obvious additional change (Fig. 5). After a quarter of an hour he was found to have lapsed into periodic respiration once again. A further injection of 0·48 g. euphyllin was given with the same effect as on the previous occasion—i.e., immediate subjective improvement and abolition of the periodic respiration. That night (four hours later) a stethograph record of the respiration showed no periodicity whatsoever. He had an excellent sleep for seven hours, and was even able to lie flat. Twenty-two hours after the injection the respiration was still regular, but twenty-four hours later the periodic breathing had returned.

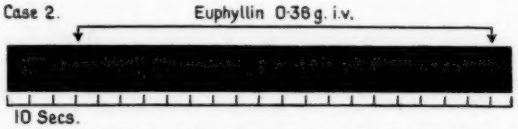


FIG. 3 (CASE 2).—Abolition of Cheyne-Stokes breathing by euphyllin.

The beneficial action of euphyllin in this patient was pronounced and maintained sufficiently long to ensure better sleep than he had had hitherto.

MODE OF ACTION

That ethylenediamine stimulates respiration was first suggested by Barbour and Hjort (1920), although acceleration of respiration from the injection of other amines had already been shown—e.g., allyl amine (Piazza 1915). In the experiments of Barbour and Hjort there was, in addition to the respiratory action, a fall in blood pressure which would be sufficient to account for increased pulmonary ventilation, a fall of pressure in the carotid sinus producing this effect (Heymans and others 1933). There is thus no conclusive proof from animal experiments that ethylenediamine stimulates the respiratory centre, although Vogl (1932) holds that this is the mode of action of euphyllin. He bases this view on (1) the almost instantaneous action of the drug in Cheyne-Stokes breathing, and (2) its action in rousing comatose patients to wakefulness. Guggenheimer (1932, 1933), however, maintains that the action on respiration is produced mainly by changes in the cerebral circulation, effected by dilatation of the cerebral arteries and aided by increased cardiac efficiency brought about by coronary vasodilatation. Guggenheimer's view is supported by Paul and others (1937) who regard a fall in venous and intrathecal pressures produced by euphyllin as suggestive of an improved cerebral circulation.

It is generally thought that the common underlying basis of Cheyne-Stokes respiration is depression

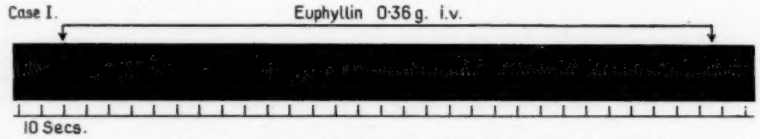


FIG. 1 (CASE 1).—Note the order of effects of intravenous injection of euphyllin: (1) the increased depth of respiration in the hyperpnœic phase; (2) the shortening of the apnœic pause; (3) the diminution of periodicity leading on to completely normal respiration.

FIG. 2 (CASE 1).—Theophyllin alone is devoid of action, which is produced, however, by ethylene diamine.

of the medullary respiratory centres. Oxygen-lack, which has been shown by Smyth (1937) to depress the medullary respiratory centre, is probably the cause of the depression in cases of cardiovascular disease such as those described above. On this assumption depression of the respiratory centre may be abolished by euphyllin by one or both of the two suggested mechanisms: (*a*) a direct stimulating action of the drug on the respiratory centre, independent of circulatory changes; (*b*) an increased circulation through the respiratory centre improving its oxygen supply.

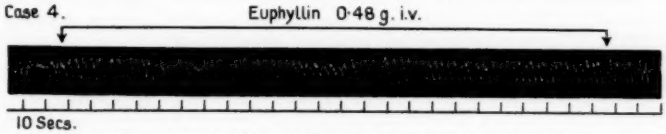


FIG. 4 (CASE 4).—Abolition of Cheyne-Stokes breathing by euphyllin.

(*a*) Direct stimulation of the respiratory centre would be expected to produce the following changes:—

1. Increased pulmonary ventilation, with resulting lowering of alveolar CO_2-tension, and lowering of the CO_2 content of arterial blood.

2. Similar changes should be demonstrable on the normally acting respiratory centre as well as on that depressed by oxygen-lack. If euphyllin caused an increased blood flow through the normal respiratory centre there would result a decreased rather than an increased pulmonary ventilation (McMichael 1937). Hence an increased pulmonary ventilation in normal subjects would favour the view of direct stimulation of the centre.

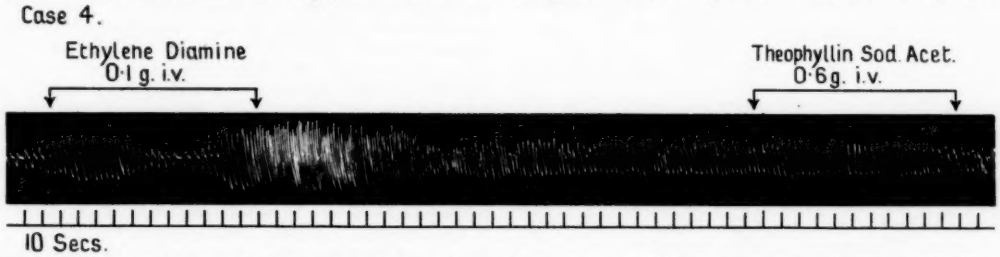


FIG. 5 (CASE 4).—Effect of 0·1 g. ethylene diamine. A great increase in rate and depth of respiration takes place followed by restoration to normal respiratory rhythm. No further action is produced by theophyllin.

INCREASED PULMONARY VENTILATION

Pulmonary ventilation can be measured by collecting and analysing the expired air in a Douglas bag over a given period of time. The measure of pulmonary ventilation suggested by Anthony (1930) and adopted by Moncrieff (1934) is the ventilation equivalent, or the pulmonary ventilation in litres per 100 c.cm. oxygen consumed. It has been shown by one of us (McM.) that the ventilation equivalent even at rest varies with changes in the cardiac output. For this reason changes in pulmonary ventilation cannot be ascribed to changes in activity of the respiratory centre unless all precautions are taken to keep the circulation-rate constant. This is best done by making all the observations under the resting conditions of oxygen consumption and in the same (usually reclining) posture. Even when these precautions are taken, another difficulty may arise: when collections of expired air are made over short periods in experimental subjects the conscious influence of the subject is apt to produce either over- or under-breathing, and these influences produce quite artificial shifts in the ventilation equivalent. Over-breathing or under-breathing can however be detected in changes in the respiratory quotient, the former tending to raise it by washing out excess of CO_2, while the latter has the converse effect. The ventilation equivalent as a criterion for measurement of pulmonary ventilation therefore breaks down in the presence of such artificial alterations of the respiratory quotient. For this reason we have adopted as our criterion for comparison the ventilation equivalent for CO_2—i.e., the ventilation in litres per 100 c.cm. CO_2 expired. This automatically compensates for any error introduced by over- or under-breathing. Comparisons were made only when the rate of oxygen consumption remained at approximately the same level before and after euphyllin, ensuring in this way a reasonably constant circulation-rate.

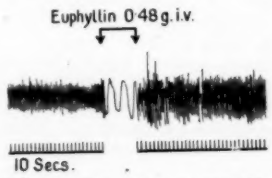


FIG. 6.—The effect of euphyllin in increasing the depth of respiration of normal type.

Table I shows the exact measurements of pulmonary ventilation made when these criteria were adopted. The increase in pulmonary ventilation is obvious in all including the normal subject.

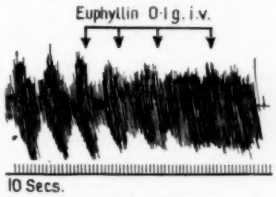


FIG. 7.—At each arrow 0·5 c.cm. containing 0·1 g. euphyllin was injected intravenously. The periodicity becomes less pronounced with successive doses and finally disappears.

In addition to these measurements on the ventilation estimated with the Douglas bag, the increase in respiration can be shown graphically. Fig. 6 shows the effect of euphyllin on a patient who was drowsy from a cerebral lesion and in whom the possibility of conscious influence on the respiration was at a minimum. The intravenous injection of 0·48 g. euphyllin was followed by an increase in the depth of respiration which was of normal type throughout the experiment.

Owing to the difficulty of getting samples of alveolar air from patients this was not attempted. In Case 1, however, arterial punctures were performed before and after giving euphyllin, and the CO_2-content of the arterial blood estimated in a van

Slyke apparatus. The blood taken during the Cheyne-Stokes phase was a mixed sample taken during apnœa and hyperpnœa.

Arterial CO_2 content in vols. per cent.	
Before euphyllin (Cheyne-Stokes breathing)	After euphyllin (Normal respiration)
53·1	48·3

The evidence, therefore, of a direct stimulating effect on the respiratory centre is unequivocal. Guggenheimer, however, maintains vigorously that

TABLE I

Euphyllin and Pulmonary Ventilation

Subject.	Before euphyllin.		After 0·48 g. euphyllin intravenously.		
	O_2 consump. (c.cm./ min.).	Ventiln. equiv. CO_2.	O_2 consump. (c.cm./ min.).	Ventiln. equiv. CO_2.	Per cent. change in pulm. ventiln.
Cheyne-Stokes breathing.					
Case 4	247	6·32	258	7·20	+14
„ 1	205	4·24	209	6·12	+44
„ 2	272	3·92	310	4·20	+7
Normal.					
J. M.	323	2·88	328	3·25	+13

Consump. = consumption ; ventiln. equiv. CO_2 = ventilation equivalent for CO_2.

any such action is at least enhanced by an increased circulation through the brain, and it is necessary to consider whether such an effect of euphyllin occurs. To this end we have made measurements of the more important circulatory functions as follows :—

1. *Pulse-rate.*—In all cases this remained constant throughout the period of injection and after respiration was restored to normal.

2. *Blood pressure.*—There was no significant change in blood pressure accompanying the euphyllin effect.

3. *Electrocardiographic changes.*—Continuous electrocardiographic records before, during, and after injection were made in Case 1. No changes were demonstrable in any of the complexes.

4. *Cardiac output.*—Using Grollman's acetylene method, with all the precautions suggested by one of us (McM.) we have measured cardiac output before and after euphyllin in one normal (J. M.) and one cardiac subject (Case 4). The results are shown in Table II.

TABLE II

Euphyllin and Cardiac Output

—	Before euphyllin.			After euphyllin.		
	A.V. O_2 diff. (c.cm./ litre).	O_2 consump. (c.cm./ min.).	Cardiac output (litres/ min.).	A.V. O_2 diff. (c.cm./ litre).	O_2 consump. (c.cm./ min.).	Cardiac output (litres/ min.).
Case 4	149	247	1·66	157	258	1·64
Normal (J. M.)	60·5	323	5·33	62·5	328	5·25

A.V. = Arterio-venous.

It is seen that there is no significant change in cardiac output with euphyllin, although the respiratory action, determined in the same experiment, was quite striking in both cases (see Table I). These figures indicate positively that the effect of euphyllin on normal or Cheyne-Stokes respiration occurs in the absence of any demonstrable change in the circulation as a whole.

It might be argued that, without changing the cardiac output or blood pressure, the drug causes a selective vasodilatation of the cerebral vessels altering the distribution of blood in favour of the brain. Such an action would produce a diminished pulmonary ventilation in normal subjects, and we have seen that the opposite effect occurs. There is thus no reason to believe that euphyllin has any local effect on the cerebral circulation.

THERAPEUTIC USE AND MODE OF ADMINISTRATION

The arrest of Cheyne-Stokes breathing is not solely a matter of academic interest, for its cessation often seems to give a great measure of subjective relief to the patients. It is during the onset of sleep that periodic breathing becomes most pronounced (Harrison and others 1934). The increased hyperpnœa may be very distressing to the patients and often keeps them awake. Restoration of normal respiratory rhythm may ensure an easy night's rest.

The drug is put up in ampoules of 2 c.cm., each containing 0·48 g. euphyllin. Vogl suggests that it should be given intravenously, and slowly. Half a cubic centimetre is injected as the respiratory movements begin to decline in amplitude, then waiting for the next period of hyperpnœa to decline the second 0·5 c.cm. is given, continuing in this manner until the whole of the 2·0 c.cm. has been injected (Fig. 7). The danger of giving the injection rapidly is that its powerful stimulating action on the respiratory centre may be superadded to the often intense dyspnœa of the hyperpnœic phase as in Fig. 5. An alternative method is to use the ampoules containing 0·24 g. in 10 c.cm. saline, and give 15–20 c.cm. of this solution intravenously, taking at least five minutes over the injection.

Suppositories are also of some value according to Vogl, but they may be effective only in mild cases. He also states that sometimes irritation of the bowel occurs from their use. Tablets by mouth may be given, but there is a general belief that theophylline may be irritating to the stomach. We have given doses up to 0·5 g. by mouth and produced the desired effect in this way, but in the event of sickness it would be better to keep to parenteral administration.

SUMMARY AND CONCLUSIONS

1. Euphyllin (theophylline-ethylenediamine) has a striking action in abolishing Cheyne-Stokes breathing.

2. Theophylline alone has no effect on Cheyne-Stokes breathing. The effect of euphyllin is due mainly to its ethylenediamine component, but euphyllin may sometimes act when ethylenediamine fails.

3. The effect is produced by a direct stimulation of the medullary respiratory centres, and it occurs in the absence of any demonstrable changes in the circulation.

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OBSERVATIONS ON THE RESPONSE OF THE PULSE-RATE TO EXERCISE IN HEALTHY MEN

By A. Bradford Hill, D.Sc., Ph.D. Lond.

H. E. Magee, M.D. Aberd., M.B. Belf.

AND

E. Major

Among those concerned with the assessment of the state of nutrition there is a fairly general desire for suitable objective tests which would make it possible to appraise the nutritional condition of children with greater certainty than is possible with the more subjective methods at present in use. The physical fitness of individuals is largely dependent on the state of nutrition, and as the response of the pulse-rate to muscular exercise is often used as a criterion of physical fitness, it was decided to make a study of the test on a selected group of physically fit individuals with a view to exploring its value for determining the state of nutrition of children. Previous workers who have employed the test have reported much variation in the response in different individuals, and in the same individual at different times.

The main objective of the present study was to determine whether the response of the pulse-rate to a standard amount of exercise is sufficiently constant in a small select group of healthy people to justify the use of the term "normal response." If individuals in perfect health were found to exhibit wide variations in their reactions, then the test could obviously not be regarded as of any practical value. If, on the other hand, the test gave promising results, it might well have a wide application. For this purpose it was essential that both the methods and the apparatus used should be simple. These conditions were fulfilled in the studies reported in this paper.

METHODS

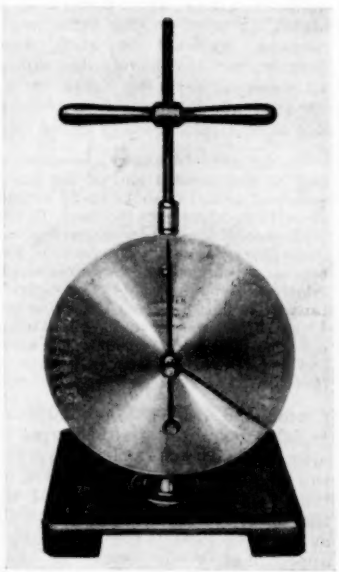
The subjects were students attending the Carnegie Physical Training College, Leeds. They were all physically fit men, aged 21–26, undergoing training for physical training instructors. Before admission to the College they had to pass a strict medical examination and to carry out satisfactorily certain physical tests. The College curriculum includes, besides lectures and laboratory work, gymnastic exercises daily and all students take part in field games and other sports such as swimming and tennis. The subjects were, therefore, all in an excellent state of training and were probably as fit a group of men as it is possible to obtain.

Two sets of observations were made, the first on 44 students during 1934–35, and the second on 29 during 1935–36.

The exercise consisted of two maximum pulls on a dynamometer, one following immediately after the other, so that the amount of exercise was relatively the same for each individual.

The *dynamometer* used was designed for work on school-children (Magee 1935). It measures the lumbar pull, the muscles involved in which—namely, those of the thigh, gluteal region, and trunk—are less likely to be specially developed in some individuals than the muscles concerned, for example, in the hand grip (see Figure). The handle of the instrument is adjustable. The level of the upper border of the patella was found after extensive trials to be the most suitable position. If the handle were not kept approximately at this level inconstant readings were obtained. In making the pull the subject stands as far as possible directly over the handle with the feet resting on the base of the instrument, one on either side of the dial, and with the knees kept straight but not rigid. The instrument is manufactured by Messrs. Salt and Son of Birmingham.

The *pulse-rate* at the wrist was counted manually. In the 1934–35 tests the resting pulse was counted for 60 seconds with the subject standing. Before the pulse-rate was taken the students had been sitting in the lecture room for an hour, had walked about 50 yards to the gymnasium where the tests were carried out, and had then stood still for five to ten minutes. The pulse counting was all done by the same observer who had had previous experience of the procedure in the course of his training. After the resting pulse had been taken the subject made two maximum pulls on the dynamometer and the observer then counted the pulse continuously for five minutes, with the subject standing, the number of beats being called out every 15 seconds and noted by an assistant. It is very probable that a beat may have been missed between the end of each 15-second period and the beginning of the next, and as the results are recorded as the number of beats per minute the experimental error was probably in the region of ± 4 beats per minute. This procedure was practically the same as that described by Woolham and Honeyburne (1927).



The dynamometer.

The results obtained in the first series showed some irregularities and it was believed that these were due partly to variation in the interval between the end of the exercise and the commencement of the counting period, an interval due to the difficulty in locating and counting the rapidly beating pulse. It was also subsequently discovered that some of the students at the end of the lecture had run upstairs to their own quarters and down again before the test was taken. Moreover no precautions were taken to keep the room free from noise and other external disturbances during the test.

In the second series of observations the procedure was improved; the subjects came straight from the lecture room into the gymnasium and the resting pulse was counted on the subjects in the sitting position after a preliminary period of rest for about ten minutes. The pulse counting in this series was done by a medical student with clinical experience. The same method was used in the subsequent determinations of the pulse-rate, and the interval between the completion of the second pull and the time when pulse counting began was determined. Precautions were taken to exclude noise and other external

disturbances from the room. The technique was, therefore, distinctly better in the second than in the first series.

The subjects were weighed and measured naked either shortly before or shortly after the exercise tests.

RESULTS

The first series of measurements was taken in December, 1934, February, 1935, and June, 1935. In all, measurements were available for 44 men, half of whom were present at each of the three dates, 19 were present twice, and 3 once only. The persons included at each date were therefore largely, but not entirely, the same. The second series of measurements was taken on a different batch of 29 students in December, 1935, and in June, 1936, the same students being tested at each date.

In the 1935–36 observations the interval between the end of the exercise and of the first 15-second period of counting varied from 19 to 28 seconds in December, and from 17 to 20 seconds in June. In the December observations two of these intervals were over 25 seconds; in the June observations four were over 20 seconds. These six sets of observations were rejected on account of this relatively long interval; the intervals in the remainder ranged from 19 to 25 in December (average 22) and from 17 to 20 in June (average 18). Deducting the first pulse-counting period of 15 seconds, the average interval between the end of the pull and the beginning of counting was, therefore, 7 seconds in December and 3 seconds in June.

Cotton and Dill (1935) found that the pulse-rate in healthy men did not alter during the first 10 seconds after exercise but that during the next 10 seconds the rate fell by about 6 per cent. compared with that immediately before the end of the exercise. It is, therefore, reasonable to assume that the pulse-rates at the 0–15 seconds interval in our second series were approximately the same as the immediate post-exercise rates.

The average measurements of the men and their variability at each test are shown in Table I. The members of the second group were on the average rather shorter and lighter than the first and their strength of pull was rather less. The differences are, however, not very large, and the amount of variability round these averages did not differ materially. The resting pulse-rate is clearly a fairly variable characteristic, as has been shown on much more extensive material—e.g., Cripps (1924). Pull ÷ weight, as the coefficients of variation show, is a more variable characteristic than weight alone, and about as variable as pull alone. In these small highly selected groups we found no correlation between the resting pulse-rate and height or weight, so that the heart-rate appeared to be independent of physique. The resting pulse-rate and the strength of pull also showed no relationship to one another. Between weight and strength of pull there was a small positive correlation.

TABLE I

Average and Variability of Measurements

Date.	No. of observations	—	Height (in.)	Weight (lb.)	Resting pulse-rate (per min.).	Strength of pull (lb.).	Pull ÷ weight.
Dec., 1934.	34	Mean.	68·5	152·0	76·6	376·2	2·5
		S.D.*	1·8	13·1	9·8	47·7	0·3
		C. of V.†	2·6	8·6	12·9	12·7	11·3
Feb., 1935.	35	Mean.	68·5	153·6	75·5	379·3	2·5
		S.D.	1·8	11·5	11·0	43·7	0·3
		C. of V.	2·7	7·5	14·6	11·5	11·7
June, 1935.	38	Mean.	68·7	153·7	79·3	366·6	2·4
		S.D.	1·9	11·9	9·3	45·0	0·3
		C. of V.	2·8	7·7	11·7	12·3	12·5
Dec., 1935.	29	Mean.	67·9	148·2	78·4	335·5	2·3
		S.D.	2·5	12·8	8·0	49·0	0·3
		C. of V.	3·6	8·7	10·2	14·6	13·2
June, 1936.	29	Mean.	68·3	150·3	72·8	321·7	2·2
		S.D.	2·4	12·7	7·6	41·4	0·2
		C. of V.	3·6	8·4	10·5	12·9	11·1

* Standard deviation.

† Coefficient of variation. These were calculated from the means and standard deviations to two decimal places.

The unweighted average of the coefficients in our five series was 0·34, which is rather less than the figure (about 0·5) reached by Cathcart (Cathcart and others 1935) in his extensive observations of employed and unemployed men and students. Between height and pull the average of our coefficients is 0·17 compared with Cathcart's figure of about 0·3 for males of the same age.

Table II shows the average reaction to exercise. In these groups there is no correlation between the initial pulse-rate and its immediate reaction to

TABLE II—MEAN PULSE-RATE AT DIFFERENT POINTS OF TIME

Initial pulse-rate.		No. of observations.	Seconds after pull.					Differences between initial and later rates.				
Group.	Mean.		0–15.	15–30.	30–45.	45–60.	60–75.*	0–15.	15–30.	30–45.	45–60.	60–75.*
1ST SERIES.												
Below 70 ..	63·5	23	80·6	77·3	71·0	66·0	63·5	+17·1	+13·8	+7·5	+2·5	0·0
70–79 ..	74·7	38	93·1	88·2	84·0	80·3	78·0	+18·4	+13·5	+9·3	+5·6	+3·3
80–89 ..	82·4	42	101·0	96·5	89·7	87·6	84·5	+18·6	+14·1	+7·3	+5·2	+2·1
90 and above	95·5	14	112·4	108·8	101·9	94·8	91·5	+16·9	+13·3	+6·4	−0·7	−1·0
Total ..	77·7	117	95·8	91·5	85·6	81·8	79·4	+18·1	+13·8	+7·9	+4·1	+1·7
2ND SERIES.												
Below 70 ..	65·2	12	87·3	72·7	69·0	66·2	63·7	+22·1	+ 7·5	+3·8	+1·0	−1·5
70–79 ..	73·8	25	94·2	80·4	75·9	72·8	72·6	+20·4	+ 6·6	+2·1	−1·0	−1·2
80–89 ..	82·8	11	99·6	88·4	85·8	82·0	81·1	+16·8	+ 5·6	+3·0	−0·8	−1·7
90 and above	94·5	4	115·0	106·0	101·0	97·0	94·0	+20·5	+11·5	+6·5	+2·5	−0·5
Total ..	75·3	52	95·4	82·3	78·3	75·1	74·0	+20·1	+ 7·0	+3·0	−0·2	−1·3

In the first set there were 4 observations between 50 and 59 and 2 between 100 and 105. In the second set there were no observations outside the groups 60–69 and 90–99. The number of observations in the first set exceeds those in the previous table because individuals are included for whom heights, &c., were missing.

* Figures relating to subsequent intervals have been excluded for brevity.

exercise. In the first series the average rise is from 17 to nearly 19 beats per minute, in the second it is about 20. If the initial rate is correlated with the absolute rise in the first 15 seconds after exercise the coefficient is nil in the first series and minus 0·22 in the second (with a standard error of 0·14). There is, therefore, no sound evidence of association between the two variables. Equality in the absolute change implies, however, that *relatively* individuals with a slow pulse-rate tend to show a greater change from their initial level than those with a fast pulse-rate.

The average levels at 0–15 seconds after exercise expressed as percentages of the average initial rates are in the first series 127 for initial rates below 70, 125 for initial rates 70–79, 123 for initial rates 80–89, and 118 for initial rates 90 or above. The corresponding percentages in the second series are 134, 128, 120, and 122 (the final percentage is based on only 4 observations).

The variation in reaction to exercise is considerable even in our highly selected sample of fit men (see Table III). In both series rather more than a third of the subjects showed an increase in the pulse-rate of between 15 and 25 beats per minute, rather more than a fifth between 25 and 35 beats, and about 6 per cent. an increase of over 35 beats. The two series differ considerably in the numbers showing a relatively small reaction, perhaps because the technique in the first series of observations was not so good as in the second.

Table II shows that there has been, on the average, a return to very nearly the initial resting rate at the end of one minute in the first series and at the end of three-quarters of a minute in the second series. It may be that the difference is due to the fact that the pulse was taken sitting in the second series and standing in the first. After the first minute the average rate remained close to the initial rate. In both series the individuals with an initial pulse-rate of 90 or over fell to an average figure a little below that high initial rate. Possibly these initial rates were raised above the real resting rates by emotional excitement and as this passed off the pulse slowed down.

TABLE III

Variability in Reaction to Exercise

Absolute difference between resting pulse-rate and rate at 0–15 secs. after exercise (beats per min.).	No. of observations in each different group.	
	1st Series.	2nd Series.
− 5−	17 (14·5)	1 (1·9)
+ 5−	26 (22·2)	17 (32·7)
+15−	42 (35·9)	19 (36·5)
+25−	25 (21·4)	12 (23·1)
+35−	6 (5·1)	3 (5·8)
+45–54	1 (0·9)	— —
Total	117 (100·0)	52 (100·0)

Percentages in parentheses.

Although the return to the initial rate is rapid on the average, this result is not found in all individuals. Table IV shows that the variation is considerable. Moreover, there is a difference between the two series; considerably more of the second series return rapidly to uniformity. Comparison of the reaction of the same individual at different tests also showed that in the first, but not in the second, series of observations there were sometimes very large differences in reaction.

Thus, in subject No. 19, 1st series, the rate was 20 beats per minute below the resting value at the 60–75 seconds interval in December, 1934, and 4 beats per minute above it in June, 1935, the resting value being the same, 80 per minute, at each test. In the 2nd series the widest differences at this interval in the same subject were for No. 14, 2 beats below the resting value of 70 in December, 1935, and 9 above the resting value of 69 in June, 1936.

TABLE IV

Absolute difference between resting rate and rate at different times after exercise.	Frequency with which difference was observed at different times after exercise.			
	15–30.	30–45.	45–60.	60–75.*
1ST SERIES.				
−20 or over −20	—	—	2 (1·7)	2 (1·7)
−19 to −15	—	2 (1·7)	2 (1·7)	2 (1·7)
−14 to −10	—	2 (1·7)	2 (1·7)	4 (3·4)
− 9 to − 5	—	5 (4·3)	10 (8·5)	14 (12·0)
− 4 to + 4	20 (17·1)	44 (37·6)	54 (46·2)	66 (56·4)
+ 5 to + 9	29 (24·8)	20 (17·1)	19 (16·2)	8 (6·8)
+10 to +14	20 (17·1)	19 (16·2)	7 (6·0)	7 (6·0)
+15 to +19	14 (12·0)	4 (3·4)	10 (8·5)	7 (6·0)
+20 or over +20	34 (29·0)	21 (17·9)	11 (9·4)	7 (6·0)
Total ..	117 (100·0)	117 (99·9)	117 (99·9)	117 (100·0)
2ND SERIES.				
−14 to −10	1 (1·9)	1 (1·9)	2 (3·8)	—
− 9 to − 5	2 (3·8)	4 (7·7)	6 (11·5)	7 (13·5)
− 4 to + 4	15 (28·9)	28 (53·8)	36 (69·2)	41 (78·8)
+ 5 to + 9	13 (25·0)	10 (19·2)	5 (9·6)	3 (5·8)
+10 to +14	14 (26·9)	5 (9·6)	3 (5·8)	1 (1·9)
+15 to +19	5 (9·6)	4 (7·7)	—	—
+20 or over +20	2 (3·8)	—	—	—
Total ..	52 (99·9)	52 (99·9)	52 (99·9)	52 (100·0)

* Figures relating to subsequent intervals have been excluded for brevity.

Figures in parentheses are percentages.

The figures of the second set are doubtless the more reliable, and attention may be confined to them. They show that, if return to the initial rate within 60 seconds is to be considered "normal," the term "normal" in these physically fit young men must be taken to include an increase (or decrease) in the pulse-rate of as much as 10–14 beats per minute. At 60–75 seconds after exercise there was only one individual whose rate was enhanced by as much 10–14 beats, but 3 minutes after the pull there were 3 persons with rates 10–20 beats above their initial rates.

Taking minus 4 to plus 4 as a negligible difference from the initial rate, 28·9 per cent. reached this level in the 15–30 seconds interval, just over half at 30–45 seconds, just over two-thirds at 45–60 seconds, just over three-quarters at 60–75 seconds, and about 90 per cent. after 2 minutes.

The distribution then widens again but the cause is not evident.

Regarding the practical value of the response of the pulse-rate to exercise, we think that these results do not suggest that the immediate reaction is very informative, since even with such a very select group of physically fit young men large variations occur. The return of the pulse-rate to normal appears to be a more suitable criterion but, as comparison between our first and second series shows, the tests would need to be done with great care if results of any value are to be obtained, and the definition of "normal" must be somewhat liberal. It is questionable whether the required degree of accuracy in technique could be obtained in school clinics, and as the test is time-consuming it could probably not be generally adopted.

SUMMARY

The pulse-rates of 73 athletic young men, aged 21–26, of excellent health and physique, were determined

every 15 seconds continuously for 5 minutes after performing two maximum pulls on a dynamometer; these rates were compared with the corresponding pre-exercise resting rates. There was no correlation between the resting pulse-rate and the height, weight, or strength of pull, so that within the population studied the pulse-rate was independent of physique and of muscular strength. In this select group only a very small degree of correlation was observed between height, weight, and strength of pull, rather less than has been noted in more numerous but less homogeneous populations.

No correlation was apparent between the initial resting pulse-rate and its immediate reaction to exercise, the absolute rise in the rate being approximately the same in individuals with slow, medium, and fast resting rates; as a corollary the percentage increase in the pulse-rate was slightly greater in individuals with a slow resting pulse than in those with a fast rate. The variation in reaction to exercise was considerable, even in such a physically select group.

In our second and more reliable series of observations, the pulse-rate returned to approximately the pre-exercise rate in from 45–60 seconds in the majority of the subjects, but some exceptions were noted. The return of the pulse to normal within this length of time was the most constant feature of the response to exercise. Even accepting this as a criterion of sound physical condition (and we have no unfit persons as a standard of comparison) it is doubtful whether the test could be successfully employed in the routine examination of school-children. Our results indicate that it requires considerable care and much time in its application.

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FLUORESCENCE MICROSCOPY ON LIVING VIRUS WITH OBLIQUE INCIDENT ILLUMINATION

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IN fluorescence microscopy two methods of illuminating the object are available, firstly, by means of a suitable substage condenser and, secondly, by oblique incident illumination.

With regard to the first, the general method in use is to employ a high power arc with suitable filters and a quartz illuminating system. Barnard and Welch (1936), however, have shown that by employing a condensed spark between magnesium electrodes in conjunction with a dispersing system and a dark ground condenser specially constructed for ultra-violet microscopy, the object can be illuminated by ultra-violet radiations; this has proved useful for the study of primary fluorescence of various bacteria. Hagemann (1937), using the arc as a light source and filters passing an ultra-violet band with a maximum of 3660 A.u., was able to demonstrate that various organisms had a great affinity for fluorescent dyes. In thin dried smears of virus-infected tissue, stained with Primuline, he has seen very minute fluorescing bodies which, on account of their shape and grouping, he regards as virus elementary bodies.*

The second method, in which oblique incident ultra-violet illumination is employed, was used for the present investigations. The optical equipment consists of an arc, a Leitz-Ultropak outfit, and a collecting lens made wholly of crown glass which, with suitable filters, allows ultra-violet light ranging roughly from 3500 to 4000 A.u. to pass. It has thus been possible to demonstrate, by fluorescence, the elementary bodies of living viruses in the cells of living, infected tissue.

A NEW TECHNIQUE

For the observation of living virus growing on the chorio-allantoic membrane of the developing chick or duck embryo, a method has been developed in which the membrane is brought into immersion contact with the under-side of a cover slip without any interference with its normal anatomical connexions. Observations can therefore be made through this cover slip with visual oblique incident illumination, or with ultra-violet light by the outfit mentioned above.

Using visual light on membranes infected with infectious ectromelia virus, the presence of inclusion bodies composed of elementary bodies can be observed in various developmental stages within cells. The arrangement of these infected cells and their relation to the capillaries allow inferences to be drawn as to the mode of infection and the manner of spread of the virus. Membranes infected with a dermal strain of vaccinia virus show from the second day onwards numerous vibrating particles within the cytoplasm of the cells. The particles may be either arranged in clumps or distributed throughout the whole of the cytoplasm.

To obtain differentiation of structure in the infected membrane by means of fluorescence microscopy, primuline as used by Hagemann and Titan yellow 2 GS (a diazoamino compound of primuline), which in solution and in the present application fluoresces with greater brilliancy, were employed. These dyes in solution fluoresce in colours varying from violet to orange according as the concentration of the dyes increases. With the fluorescence resulting from high concentrations these colours are very impure, the wave-lengths emitted in each colour covering a broad range of the spectrum.

When the dyes are applied to infected membranes they are taken up by various structures in such a way as to produce an image of high colour contrast, due either to the varying concentration of the dye as a whole or to a selective affinity to one or other constituent of the dye which, in the case of Titan yellow, is a mixed diazo compound of dehydrothio-*p*-toluidine sulphonic acid. It is noticeable that the green is missing and that with most structures the colours exhibited appear to be purer than the colours emitted by the solutions alone.

If egg membranes with ectromelia lesions are treated with dye and then examined with oblique incident ultra-violet light a fluorescent picture with sharp contrasts is seen. The inclusion bodies appear as mauve structures within pale blue cells against a violet background consisting of normal structures which, with few exceptions, have not taken up the dye. Some large intracellular granules and the nuclei of some of the infected cells, leucocytes, red

* See *Lancet*, July 10th, 1937, p. 91.

blood corpuscles, and mononuclear cells (? histiocytes) appear in colours varying between bright orange and brownish-orange.

On further examination of the inclusion bodies with the highest N. A. objectives (Ultropak) available the elementary bodies can be detected as bright blue particles on a mauve background representing the matrix. The mauve colour is probably due to the combination of light emitted from out-of-focus granules together with that from the matrix. This is suggested by the fact that by focusing into lower planes the inclusion bodies appear more bluish in colour, whilst the granularity disappears owing to loss of contrast.

On the application of dye to vaccinal lesions it is found that, as in the case of ectromelia, cell structures in relation to the above-mentioned vibrating particles can be differentiated. A similar affinity for the dye is shown by these particles which also appear as light blue granules against a mauve background. In dead cells where the vibration has ceased, their presence is indicated by light blue areas and the nuclei appear as orange-brown structures.

There is little doubt that these granules are true virus elementary bodies and that they correspond to Paschen's elementary bodies. Their vibratory behaviour, not noticeable before the second day of infection, suggests a developmental phase following a stationary one as in the case of psittacosis (Bedson and Bland 1932, Bland and Canti 1935).

I am indebted to Mr. J. Smiles for his constant help, particularly in the development of the optical system.

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BRITISH MEDICAL ASSOCIATION

SECTION OF SURGERY

Prof. P. T. CRYMBLE, the president, was in the chair at a meeting of this session when a discussion on

Obstructions of the Common Bile-duct

was opened by Prof. E. R. FLINT (Leeds). He said that obstructions of the common bile-duct may be partial or complete, with jaundice, but that jaundice does not necessarily imply common duct obstruction. Partial obstruction on the other hand may give rise to no ordinary clinical signs, but only to an increase in the plasma bilirubin which can be detected by the van den Bergh test. This obstruction might be either intra- or extrahepatic. Prof. Flint considered that the more common are: stone and its complications, pressure on duct from without by simple or malignant pancreatic lesions, spasm of the sphincter of Oddi. The problem of diagnosis was not great, stone in the common duct, carcinoma of the head of the pancreas and chronic pancreatitis each having their distinctive features. In atypical cases any one of the clinical signs or symptoms might be interchanged between the diseases, making the diagnosis difficult. It was difficult also to determine whether the origin of jaundice was intra- or extrahepatic; mechanical obstruction and cholangitis could produce similar liver changes. A painless jaundice with bile in the duodenum suggested an intrahepatic lesion; such a jaundice was distinctly yellow and without much itching. The marked retention of tetra-iodophenophthalein injected suggests an intrahepatic lesion. It seemed inevitable that if operation was suggested for all cases of suspected obstructive jaundice some unnecessary operations would be performed. On the other hand, some patients would be relieved by the finding of a stone where malignant disease had been suspected. Of pancreatic obstructions to the duct 20 per cent. would prove to be simple. The effect of obstruction was to produce dilatation of the duct; it became bluish, and the bile in it is dark and inspissated in obstructions from without. In stone the duct was thick, pinkish yellow, and contained thin yellow or muddy fæcal-odoured bile. In 5 per cent. of cases there would be found "white bile," the signal of a serious hepatic injury. In the liver the injury would vary from mild central necrosis to acute atrophy; the best guide to serious damage was the serum bilirubin. Patients with lesions of the liver tended to have a prolonged coagulation time and to bleed. The blood-urea rose, bile salts disappeared from the blood and urine, casts and albumin appeared in the urine, and the patient vomited altered blood. Ascites and splenic enlargement might result from the fibrosis, and a stone in the ampulla might cause back pressure on the pancreas with all its effects. Work done at the Mayo Clinic had shown the presence of anæmia and anoxæmia of the stagnant type with an effect on metabolism which might well be the reason for the success of glucose therapy.

Operation should be carried out in these patients in one to two weeks from the onset of symptoms; this gave ample time for the essential pre-operative preparation which consisted in providing water, salt, sugar, and blood to rectify as far as possible the disturbances produced by the disease. Water, salt, and sugar would be given by the intravenous drip method. The water balance must be watched and, if necessary, a blood transfusion given to provide protein. Apart from this the benefits of a blood transfusion were to raise the peripheral blood pressure, diminish post-operative bleeding, replace lost blood, and raise the hæmoglobin content, and therefore the oxygen-carrying power of the blood. The transfusion was best given by the drip method. Calcium was useful, as apart from its effect on bleeding it had a beneficial action on the liver. In operating the best practice was to do as little as possible; the duct should be decompressed slowly with a syringe and needle, cleaned, and, after dilatation of the ampulla, drained externally with a T tube. The common duct should be opened if the duct is dilated, altered in colour, thickened, or if the pancreas is hard or gritty. Prof. Flint said that the anæsthetic of choice is spinal, the fall in blood pressure being countered by Icarol, and sufficient gas and oxygen to keep the breathing fairly deep. Spinal anæsthesia gives complete relaxation, and has no toxic action on the liver or kidneys. Post-operative treatment should be on the lines of pre-operation routine. After the operation 10 per cent. CO_2 in oxygen should be given until the patient takes 4 or 5 deep breaths, every quarter of an hour for 24 hours. The results in operations carried out using this technique have shown in Prof. Flint's experience a mortality of 4·7 per cent. in 84 cases of stone in the common duct.

Mr. HOWARD STEVENSON (Belfast) endorsed many of Prof. Flint's remarks. He emphasised particularly external drainage of the common duct and dilatation of the ampulla by weighted gum elastic probes in preference to metal sounds.

Mr. G. GORDON-TAYLOR (London) declared himself in complete agreement with the opening remarks. He deplored the growing tendency to explore the common duct as a supplement to cholecystectomy, alleging that it is performed in 40 per cent. of cases of this kind. He favoured the external method of drainage with T tube. He spoke of the bacteriology of the bile mud; the Welch bacillus was the cause of death in 2 cases known to him. He advocated the use of Cylotropin and pre-operative irradiation of the splenic area to diminish bleeding in these cases. In conclusion he expressed the feeling that more courage was required in treating malignant disease of the common duct regions.

Prof. A. H. BURGESS (Manchester) endorsed Mr. Gordon-Taylor's view that choledochotomy was too frequently performed. In a normal pancreas the common bile-duct, he said, is easily palpable in its whole extent. Spinal anæsthesia seemed, he thought, to be followed too frequently by chest complications to be recommended in these cases.

Mr. N. C. LAKE (London) strongly favoured spinal anæsthesia; complications could be prevented by the use of CO_2 as described by Prof. Flint. He said the discussion had prompted him to the view that the gall-bladder might be the focus of infection in some cases of arthritis.

Prof. C. F. M. SAINT (Capetown) said he found Murphy's button useful in cholecystenterostomy in promoting hæmostasis.

The PRESIDENT described a case of obstruction of the ampulla due to an adenoma in which local excision gave a good result.

Short Papers

Prof. L. R. BRAITHWAITE spoke of some points in *Duodenal Regurgitation*. He said that 80 per cent. of the regurgitant fluid into the stomach was pancreatic juice, a much more constant constituent than bile, which was sometimes even absent. The action of bile on the stomach is threefold: it slows gastric peristalsis, lowers the gastric acidity, and arrests peptic digestion. It was therefore a "rest factor" for the stomach, and as such one would think it should be beneficial in duodenal ulcer. The operation of cholecystgastrostomy might therefore be of benefit in cases of duodenal ulcer without stenosis. This operation did not replace the natural regurgitation as it did not ensure the flow of pancreatic juice into the stomach; to ensure this one would have to close the duodenum at the duodenojejunal junction and do a gastro-enterostomy. This operation had not yet been performed; but cholecystgastrostomy enjoyed success up to a point. It relieved the duodenal symptoms entirely, but they unfortunately recurred in between 18 months and 2 years.

Mr. A. K. HENRY (London) in speaking of *Burns* preferred the dry tannic acid method of treatment. Its drawback, he said, was that sepsis was liable to occur at the edges of the hardening crust; this liability he had greatly diminished by painting the skin edges and the patients' fingers with 1 per cent. brilliant green in absolute alcohol daily. As to shock one hour's delay only was permissible before instituting tannic acid treatment; a longer wait only made the shock more profound. From the fourth to the tenth day toxæmia was a danger. Gastric acidity was very high, occult blood was present, and histamine in the blood was four times as great as normal. He suggested very large doses of alkali to counteract this.

Mr. J. G. YATES-BELL (London) described the *Steinach operation for the relief of prostatic symptoms*. He said that the operation produced its effect by a vasomotor reflex from pressure on the ganglion, and also later by affecting the hormone secretion of the testes. In 28 cases, 7 of which were excluded as they had other minor operations performed as well, he had 12 successes and 4 failures, the rest being doubtful. The indications for this operation were: early cases with few symptoms, early cases with residual urine under 4 oz., cases complicated by vesical calculus. The contra-indications were poor kidney function and atrophic testes.

Prof. E. W. ARCHIBALD (Montreal) maintained that *spasm of the sphincter of Oddi* was responsible for some cases of obscure epigastric pain and attributed it to an imbalance of the parasympathetic system. Clinically there are three types of case: (1) those who have pain sometimes vague in nature following cholecystectomy; (2) cases of recurring pancreatic œdema and pancreatitis; (3) cases of cholangitis. At operation bile sand and slush was found in the common duct. The operation of cutting the sphincter was performed through an incision in the duodenum, a special guide having been previously passed down the common duct. According to Prof. Archibald the sphincter does not regenerate.

SECTION OF OBSTETRICS AND GYNÆCOLOGY

Prof. C. G. LOWRY (Belfast), the president, took the chair at a meeting of this section when a paper on the clinical value of

Prontosil and Similar Compounds in the Treatment of Puerperal Infections

was read by Mr. G. F. GIBBERD (London). His cases were those admitted to the isolation block of Queen Charlotte's Hospital in 1936–37, and he compared their progress with that of similar cases admitted in 1934–35. Prontosil and Streptocide (sulphanilamide) had both been used since the beginning of 1936. Prontosil had been given intramuscularly in doses of 0·5 to 1·5 gramme or 20–60 c.cm. and orally in doses of 2–4 g. or 6–12 tablets daily. Maximum doses had been given to severely ill patients, and a few had developed cyanosis, but the treatment had been continued without untoward effect. Analysis showed that the gross mortality in the 1934–35 group was 20 per cent., whereas in the 1936–37 group it was only 4·5. The virulence of the hæmolytic streptococcus depended on its invasiveness, and it should be noted that the infection was limited to the birth canal in 47 per cent. of the 1934–35 cases, and in 66 per cent. of the 1936–37 cases. The difference must have been due either to diminished virulence in the streptococcus during 1936–37, or to the new treatment given. The mortality-rate in proven septicæmia (excluding general peritonitis) was 40 per cent. in patients who did not receive the new drugs and 20 per cent. in those who did. The incidence of septicæmia before admission did not greatly differ in the two groups, and this was evidence that there was no considerable difference in the invasiveness or virulence of the prevalent streptococcus in the two periods. In non-fatal cases where an actual inflammatory mass had been demonstrated outside the limits of the birth canal, the illness had been decidedly shortened since the use of prontosil, and Mr. Gibberd regarded this the most convincing piece of direct evidence that it was beneficial. The improvement in the mortality-rate was associated with a decrease in the invasion of tissues rather than with a greater tendency to resolution of the disease once widespread invasion of tissues had occurred. There was every reason to continue to employ the new remedies until their value or otherwise was more firmly established.

Miss D. B. BROWN (Belfast) analysed 30 cases treated in the isolation block at Belfast. In 19 cases of local infection, 8 of which were very serious, prontosil had been definitely beneficial. Of 7 patients with septicæmia, 2 had died, and these might have been inadequately treated. One had previously had a nephrectomy for renal tuberculosis and the other had had a mixed infection. When necessary, large doses had been given, one patient having received 189·4 g. in 36 days and another 186 g. in 31 days. Cyanosis had appeared in 2 cases of septicæmia, but it seemed to bear no relation to the amount of the drug given. Prontosil apparently had a definite value in preventing abscess-formation when given in cases of acute mastitis.

Mr. L. CARNAC RIVETT (London) wished to emphasise certain points in Mr. Gibberd's figures. He had grouped together the serious cases of septicæmia and peritonitis yearly from 1932 and was able to demonstrate a sudden drop from an average mortality of 71 per cent. to one of 27·3 per cent. since the use of prontosil. He showed temperature charts of severe cases with a fall in temperature in 2–5 days. He drew attention to the possibilities of prontosil used locally.

Prof. H. J. DREW SMYTHE (Bristol) had had a year's experience of prontosil. Of 23 cases of puerperal infection, mostly mild, roughly half had received prontosil and the mortality had been about the same as in those treated without it. He had been impressed however by the increased rapidity of cure in cases that had received prontosil. Sulphæmoglobinæmia had caused him no real anxiety and always cleared up on ceasing to give the drug; the important warning signs of this complication were headaches and loss of appetite. He considered that drugs of the sulphanilamide group were not bactericidal but rendered bacteria more vulnerable to attack by leucocytes or else stimulated the leucocytes in some way.

Dr. BETHEL SOLOMONS (Dublin) hoped that the marvellous effects of prontosil would not give the practitioner of midwifery a false sense of security. Prevention of sepsis was what mattered most, and this could only be obtained by a thorough knowledge of obstetrics acquired from skilled teachers.

Prof. J. CHASSAR MOIR (Oxford) said there were possible dangers in prontosil administration which had not been mentioned, such as interference with hæmopoiesis. Its routine prophylactic use was unwise. Prontosil was effective in pyelitis of pregnancy and in most cases the urine could be rendered sterile in five days.

Dr. A. SHERWIN (Melbourne) asked if prontosil would be likely to help in cases of *Bacillus welchii* infection.

Mr. GIBBERD, in reply, said a few cases of *B. welchii* infection were admitted to Queen Charlotte's but the vast majority of puerperal infections were due to hæmolytic streptococci. As regards the mode of action he thought that sulphanilamide was liberated in the blood stream and acted as a bactericide. Methæmoglobinæmia was caused by prontosil and not by magnesium sulphate. In the presence of magnesium sulphate methæmoglobin was changed to sulphæmoglobin and this took much longer to eliminate—a state of affairs that might be serious where there was anæmia. The results of prontosil therapy were surprisingly good, but he must maintain his doubt whether a decrease in virulence in the streptococcus might not partly account for them.

Abortion

Mr. P. MALPAS (Liverpool) had calculated that about once in 100 pregnancies a woman was encountered who had had three or more abortions, these being attributable to recurring causes rather than accidental or random ones. Cases showing recurrent abortions were allied in some way with those of recurring stillbirths and toxæmias of pregnancy with accidental hæmorrhage. He had studied 115 fraternities containing recurrent abortions and stillbirths with regard to abnormalities; he had found either lesions of the developing embryo or chronic maternal disease in 65 cases, but no demonstrable abnormal condition in the other 50. There appeared to be a recognisable ætiological factor in roughly half the cases. He mentioned two cases in which a woman had had a successful pregnancy by one husband but a series of abortions by another, thus suggesting a possible cause in the male partner. As regards treatment, though the experimental evidence was in favour of wheat-germ oil it was certain that vitamin-E deficiency was not a constant factor in recurrent abortion. Vitamin C was important in maintaining the viability of embryos. He regarded treatment with corpus luteum hormone (progestin) as the most effective remedy, but more clinical data were needed. Arsenic had been found helpful, given as novarsenobillon, in non-syphilitic cases. Further knowledge of the ordinary metabolism of the early human embryo was necessary; it died either from maldevelopment or interference with early nutrition.

Mr. H. C. HARDY GREER (Belfast) said he found the corpus luteum preparation Proluton most helpful in cases of recurrent abortion and he was encouraged to persist in its use.

Prof. T. D. O'DONEL BROWNE (Dublin) said that, contrary to what is generally taught, the proportion of abortions due to syphilis is small. In cases of actual bleeding an adequate dose of proluton would stop the hæmorrhage if given before the ovum was dead.

Dame LOUISE MCILROY (London) said that though abortions were not often due to syphilis stillbirths often were. She treated cases of repeated abortion with a daily oral dose of corpus luteum and thyroid extract. She had had success in two cases of repeated abortions by using wheat-germ oil. Death of the ovum was due to some complicated metabolic cause.

Dr. J. J. HOLLAND (Perth, W. Australia) said that in breeding animals it was found that a healthy female might always abort to a certain male. The paternal factor in human cases should be further investigated.

Hysterosalpingography

Mr. V. B. GREEN-ARMYTAGE (London) spoke on the obstetrical and gynæcological importance of hysterosalpingography and its advantages over simple insufflation. Insufflation did not provide information about both tubes or about the site of tubal occlusion or other abnormalities in the Müllerian tract, and treatment and prognosis depended on accurate knowledge. An important question arose as to the condition of the tubes after peritonitis due to appendicitis, either before or after marriage, and after an extra-uterine pregnancy when the extravasated blood might have blocked both tubes. The state of the tubes after salpingitis due to any cause should be investigated if the patient wished to know about the possibilities of pregnancy. Salpingography could not lie and he had had no regrettable results. In a series of 300 cases of sterility he had found that in 40 per cent. blocked tubes were responsible. The injection of up to 20 c.cm. of Lipiodol was done in the consulting-room and no anæsthetic was given. It was important that the lipiodol should be at body temperature. The patient was radiographed ten minutes afterwards and walked out. If Mr. Green-Armytage found the

fimbrial end blocked he operated and pregnancy had followed in 20 per cent. of his cases. If the block was at the cornu it was worth implanting the tubes in the uterine wall. He always did a salpingography after operation to prove the patency of the tubes; the psychological effect for a woman of knowing there was no reason why she should not become pregnant was very important.

Dr. SOLOMONS said he agreed with Mr. Green-Armytage's views. He himself used Ethytol and had had no accidents except mild irritation of the peritoneum in one case. He always took a second radiogram ten minutes after the first, by which time any apparent blockage due to spasm would have disappeared.

Prof. CHASSAR MOIR asked whether there had been any untoward symptoms. He thought he had seen what looked like the shadow of lipiodol in the pelvic veins in one of the radiograms shown by Mr. Green-Armytage.

The PRESIDENT said he had occasionally seen collapse after the injection of lipiodol. He regarded acute appendicitis as an important cause of sterility.

Mr. GREEN-ARMYTAGE, in reply, said he thought the type of instrument with apertures at the sides might cause collapse from sudden distension of the cervical canal. He used one with a distal aperture. In over 800 salpingographies he had given an anæsthetic (Evipan) only twice. He performed it 5–7 days after a period. The patient, being conscious, could complain of any pain felt, and this might be helpful. The pain was never acute, and there had been no case of oil or air embolism.

SECTION OF DISEASES OF CHILDREN

AT a meeting of this section, with Dr. H. MORLEY FLETCHER (London) in the chair, a discussion on

Enuresis

was opened by Dr. ROBERT HUTCHISON (London), who said that this condition, as Bacon said of medicine in general, is "a subject which has been much laboured but little advanced," for we are still very ignorant of its causes and mechanism and largely helpless in its treatment. He limited enuresis to bed-wetting and did not regard it as pathological until the age of three. The functional characteristics are important although he maintained that the children show no recognisable psychoneurotic peculiarities and generally come from normal homes. He dismissed high acidity of the urine, phimosis, threadworms, enlarged tonsils, and adenoids as contributory causes, although he agreed that removal of the adenoids might be the deciding factor in terminating the condition. He called attention to the group of cases with nocturnal polyuria and wondered whether they were due to a functional disability of the kidney or to a vasomotor instability. Enuresis usually disappeared before puberty although it might persist much later. He summed up the essentials of prognosis in the words of a French writer; the enuretic is "socially dead." Dr. Hutchison's advice on treatment followed classical lines as to general management; sphagnum moss or a rubber urinal counteracted unpleasant effects. Belladonna has fallen into wrongful disuse, as it improved the condition clinically, although its mechanism was not understood. Ergot, ephedrine, pituitary extract, and other endocrines had proved of little help. The passing of sounds has no justification. There remained psychotherapeutic methods; suggestion and hypnotism might prove useful in certain cases, but more severe practices, such as Freudian analysis, were di proportionate to the object.

Dr. S. GRAHAM (Glasgow) emphasised the importance of excluding organic disease, notably pyuria, chronic interstitial nephritis, diabetes mellitus, and diabetes insipidus. The evidence that spina bifida, calculi, acidity, phosphaturia, and phimosis lead to a bed-wetting was not substantial. There was no typical mental make-up among enuretics, and their sleep characteristics varied, although the wetting usually took place soon after sleep began. Psychological treatment held out the greatest hope and should produce an increasing number of cures.

Dr. R. MARSHALL (Belfast) asked what caused the persistent occasional enuresis in a boy when he goes away from home, in contrast to the effect on the average enuretic of admission to hospital; and whether there was any recognised connexion between this type of enuresis and epilepsy. In his opinion enuresis was connected with two types of bad mother: (1) too fussy, (2) too careless.

The PRESIDENT did not agree with Dr. Hutchison's age limit, holding that control of the bladder should be established before three years of age. He advocated inquiry into the day habits of an enuretic; should frequency be a factor the child should be taught to hold urine in the bladder for gradually increasing periods of time, up to three hours. If this training was done well, the night habits would also improve. He mentioned the onset of enuresis in adolescence which he attributed to development of puberty, and also called attention to enuresis following severe measles and typhoid. Belladonna was the only useful drug, but must be used in sufficient doses.

Dr. E A. BENNETT (London) outlined the psychological point of view. He asked that the total personality should be taken into account and that the parental relations should be reviewed. These children absorbed "upsets" in the home and then developed enuresis. The child must be taught to take his own responsibilities and should keep a diary, in which he initialed his own reports. Hypnotism was often used but was superficial. Freudian analysis should be reserved for the exceptional child. Adler's methods were preferable and the attitude of the child towards his parents should be changed towards independence. Explanation of dreams might be of use and any method whereby the child was made to see that no guilt was involved but only an emotional state would finally produce the desired cure.

Dr. R. E. STEEN (Dublin) associated himself with Dr. Bennett as regards the "blame factor." He advocated the cutting down of solid food at tea as well as fluids, and belladonna as the most useful drug.

Prof. S. BARLING (Birmingham) also agreed with Dr. Bennett. It was important for the child to take his own responsibility. Close coöperation with the psychotherapeutists was desirable.

Dr. W. R. F. COLLIS (Dublin) asked that a greater interest should be taken in the cause of the condition.

Dr. A. A. MONCRIEFF (London) said that babies nowadays are overtrained and that parental interest in psychology frequently produces untoward effects.

Dr. H. K. MCKERNAN (London) asked what could be done for the child from the poor home who cannot be induced to attend a child guidance clinic.

Dr. T. H. CROZIER (Belfast) agreed that the most difficult cases come from poor homes, and that the parents need treatment as well as the child.

Dr. D. C. R. R. JENKINS (Belfast) described the distress of the boy who suffers from enuresis on entering his public school. The condition frequently disappeared as he gained in importance. He had found the use of a diary and the administration of belladonna gave the best results.

Dr. HUTCHISON, in reply, said that in persistent occasional enuresis a return in an almost cured

case might be due to any mental or physical upset. He did not approve of the attempt to produce early dryness and believed that the final issue was thus only evaded. He welcomed Dr. Bennett's remarks but did not himself believe that parental disharmony had anything to do with the condition; in his opinion exaggerated weight was attached to this factor. Psychotherapeutic treatment would stand or fall by its results. There was danger that the use of a diary would lend too much importance to the condition in the child's mind; rather should it be realised that if a child is unhappy his bladder may become out of control. Dr. Hutchison welcomed Dr. Steen's suggestion of cutting down the food intake and agreed with Dr. Moncrieff that the modern child has been too much studied.

Prof. BARLING read a paper on the diagnosis and treatment of

Tuberculous Cervical Adenitis

He pointed out that not only the incidence of this condition but also the severity had diminished during the last thirty years. Clinical experience had shown that this disease caused much ill health but was rarely lethal, and it was unusual for generalised tuberculosis to follow. Under the age of two years prognosis was more grave, and excision should be avoided where possible, except with extensive involvement of the skin. In older children the outlook was better, and once the local condition was mastered reassurance might be given as to generalisation. He held that a combination of tuberculous and septic infection, both of low grade, resulted in an essentially localised lesion. In the early stages the condition differed little from simple chronic adenitis, but as time progressed matting of the glands made a tuberculous diagnosis more probable. Softening of the glands or involvement of the skin made the diagnosis almost certain. In the early stages pain might be present but later was absent, unless secondary infection or skin involvement occurred. Ætiology included bad environment, poor nutrition, and local foci of infection in tonsils, adenoids, teeth, or skin. Rarely, infection resulted from a case of open pulmonary tuberculosis in the household. Infected milk more usually produced infection of the thorax or abdomen. Treatment by various physical agents had been increasingly used in the post-war years, and advocates of radium, X rays, and various forms of light therapy all claimed a high percentage of successes. Prof. Barling usually treated the early cases, with unbroken skin, with a mercury vapour lamp in increasing dosage; to achieve complete cure might take a year or more, but in most cases resolution might be expected. Especially good results were obtained between the ages of 2 and 10. Among these the younger the patient and the more recent the infection the greater were the advantages of non-operative methods. Cases in adolescence did best with light treatment before operation, especially where sinuses were present. Light lessened the local œdema and infection in and around the glands, and when used after surgery had a favourable effect on missed outlying glands, thus guarding against recurrence. Aspiration might suffice for a tiny area, followed by prolonged light treatment, but repeated aspiration usually ended in sinus formation and deep sepsis. Surgery was indicated for (1) extensive glands breaking down; (2) when glands appear for the first time in adolescence; (3) when non-operative treatment has been carried out and no further improvement had taken place. A high degree of surgical skill was needed for this type of case.

Dr. MARSHALL raised the question whether the decreased incidence of abdominal tuberculosis had not coincided with that of cervical adenitis.

Dr. HUTCHISON agreed that infected tonsils were frequently an early cause of this condition and advocated tonsillectomy, followed by six weeks at the seaside. Should the glands not disappear, then excision should be advised. In his opinion light treatment was time-consuming and probably as expensive in the long run as more drastic measures.

Prof. J. MORLEY (Manchester) advocated complete excision. He deprecated curettage as this predisposed to reinfection of adjacent groups of glands.

Prof. BARLING, in reply, agreed that the pendulum against surgery had swung too far, but wished to emphasise the necessity for the best surgical skill.

Dr. MONCRIEFF read a paper on the

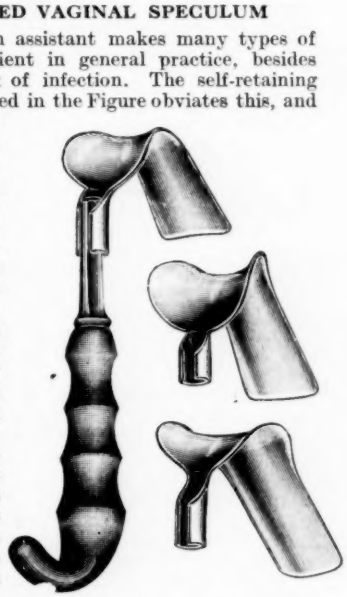
Use of Thyroid for Premature Babies

He had followed the suggestion of Dr. E. Pritchard that thyroid might speed up the maturation of premature babies, as it had done experimentally in tadpoles. It was not given to replace a deficiency. He showed charts to illustrate the effect on weight, mortality-rate, and temperature. In a controlled experiment the mortality-rate in premature babies receiving daily 1/20 grain of thyroid extract per lb. body-weight was a third that among the untreated babies. A full report on this work would be published in the near future.—Dr. COLLIS had also found thyroid useful for premature babies.

NEW INVENTIONS

AN IMPROVED VAGINAL SPECULUM

THE need for an assistant makes many types of speculum inconvenient in general practice, besides adding to the risk of infection. The self-retaining instrument illustrated in the Figure obviates this, and because of the absence of all screws and hinges it can be easily cleaned, and has a long life. It consists of a heavy handle and three blades of different sizes to fit into it. The medium-sized blade is the one most generally used, but there is no difficulty in changing it in the course of an operation. The weight of the handle is enough to retract the wall of the vagina and for it to be retained as long as desired, even in restless patients. The absence of an anterior blade allows the cervix to be freely drawn down and affords a wide view, but if needed an additional ordinary speculum may be used in the ordinary way. The instrument fits into any steriliser or doctor's bag. It has been made for me by the Surgical Manufacturing Co., London, W.1.



S. JASWONSKY, M.D.

Kovno, Lithuania.

REVIEWS AND NOTICES OF BOOKS

Physiological Basis of Medical Practice

By C. H. BEST, M.A., M.D., D.Sc. Lond., F.R.S. Canada, F.R.C.P. Canada, Professor and Head of Department of Physiology, Associate Director of the Connaught Laboratories, Research Associate in the Banting-Best Department of Medical Research, University of Toronto; and N. B. TAYLOR, M.D., F.R.S. Canada, F.R.C.S. Edin., F.R.C.P. Canada, Professor of Physiology, University of Toronto. London: Baillière, Tindall and Cox. 1937. Pp. 1684. 45*s*.

As the authors of this book point out, there is now a growing conviction that "morbid physiology" has been neglected in the past in favour of morbid anatomy, though the neglect has been due to lack of knowledge rather than lack of interest. A book by Krehl, published thirty or forty years ago, which ran into several editions (the last appearing in 1916), dealt with the more physiological aspects of pathology, stressing their importance but hampered throughout by a paucity of known facts. Those who attempt to-day to correlate physiology and medicine are embarrassed by such a wealth of more (or less) scientific information, that protagonists of this research are pleading for a fresh start at the other end, digging back channels to receive and direct the oncoming flood. This book by Best and Taylor is essentially a text-book of physiology which does not stop at a description of the normal, but displays fully the consequences of functional derangement. It is large and comprehensive enough to do justice to the scientific method, and the result is impressive. After all, the essence of physiological research is not mere observation but experiment, and experiment involves the study of a tissue, organ, or system under artificially controlled conditions. It is inevitable that investigation should progress from the isolated tissue to the whole organism, and from the lower animal types to the higher, and that the artificial environment should gradually proceed from the purely physical to the physiological. An artificial physiological environment is a pathological condition, and the modern physiologist finds himself more and more often coming into contact with such conditions. It is, of course, impossible and undesirable to lay down any law of progress; many important discoveries have been evolved in precisely the reverse direction, but the paths of the clinical and scientific investigator intersect at a point which is moving steadily and ever more rapidly in one direction. It is increasingly important, therefore, that we should periodically be presented with a bird's-eye view of the situation, and this has been skilfully provided in this work which is written primarily for students. The style is clear, direct, and logical. The seeker after sensation will be disappointed, and also those who delight in subtle argument. There is no space in the seventeen hundred pages for anything but the transfer of information from authors to reader; and it is a merit that it has been made readily assimilable.

Most of the work is straightforward physiology and biochemistry, as the title suggests, and it is quite up to date. There is, however, a commendable absence of tag ends of recently acquired information which would tend to break the continuity of the text. Indeed, this might be open to the criticism of being a little dogmatic, if it were not for two features which enormously increase the scope of the book. One is an excellent system of cross references, and the other the list of original papers and monographs which are arranged under chapter headings and occupy the last hundred pages. The full titles of these are given and the authors are not always specifically referred to in the text, which is not overburdened with names, and is moreover unrestricted by any obligation in the way of exact quotation. The reader is given an interpretation which he can readily understand and can easily check by using the bibliography. A brief account of structure is introduced where necessary, and free use is made of small print in describing experimental methods and in presenting the background. The keynote of the book is comprehensiveness in relation to the subject as a whole, without the confusion which is apt to result from a mere catalogue of detail.

Diseases of the Colon and Rectum

Diagnosis and Non-Operative Treatment. By GOTTWALD SCHWARZ, M.D., Professor, University of Vienna; JACQUES GOLDBERGER, M.D., Consulting Physician, Carlsbad; and CHARLES CROCKER, M.D. London: H. K. Lewis and Co. 1937. Pp. 540. 40*s*.

A professor of radiology and two consulting physicians, working in collaboration, have much of interest to say about diseases of the colon and rectum. Nearly 250 of their pages are devoted to diagnosis, including an account of the physiology and movements of the large intestine. They describe a new type of "deplicoptic" proctosigmoidoscope which has an optical arrangement, something like that of a cystoscope, giving an exceptionally clear and enlarged field of view. It is a long instrument (35 cm.) and of a diameter no larger than that of the ordinary child's sigmoidoscope (13·5 mm.). They claim that it is passed more easily than the usual adult sigmoidoscope; air inflation can be used, but more commonly a continuous stream of warm water keeps the bowel distended and the field clear. Certain of the coloured plates (notably V and VI) suggest that the view of a rectosigmoid carcinoma given by this instrument is very different from that to which we are accustomed in the air-inflated sigmoidoscopes. It seems to us a moot point whether in endoscopy of the rectum and the pelvic colon a greatly magnified view is an advantage to the person with normal vision, and we question also whether water inflation is likely to give a true and easily recognisable picture of the mucous membrane of a viscus which is normally in a relatively dry state. Chapter V is devoted to laboratory examination of the fæces, and includes an excellent account of the protozoa which may be found in the stools. In Chapter VI we find a full account of diagnosis by X rays, and are introduced to the term "irrigoscopy" for the barium enema controlled by fluoroscopy. A large series of radiograms illustrate this chapter, and the radiographic appearances of the colon in such conditions as ulcerative colitis, megacolon, diverticulitis, carcinoma, and polyposis are exhaustively discussed. General methods of treatment by diet, massage, and hydrotherapy, both external and internal, are described, including various forms of electrical treatment. The medical treatment of the large number of diseases of the colon is given in great detail, particularly of the dysenteries and the various forms of colitis, megacolon, and diverticulitis. The authors have written helpful sections on diarrhœa, muco-membranous colitis, constipation, and visceroptosis. The final short chapter on diseases of the anus and rectum deals with

some conditions which scarcely come within the province of a physician, such as fissure, fistula, and abscess.

A few words and phrases are curious: for instance, "tuberculotic" is used as an adjective (p. 494), and in the final paragraph of the book we read "The application of the enterocleaner in cases of dyschezia . . ." In the main the authors have kept very fairly to their medical viewpoint and have indicated the conditions for which surgery is advisable. Since the diseases discussed include many, such as diverticulitis, colitis, and proctitis, which come under the survey of both surgeons and physicians, all clinicians will read it with profit.

Die Prophylaxe der Schlafstörung

Von Dr. med. habil. PAUL VOGLER, Dozent an der Universität, Berlin. Leipzig: Georg Thieme. 1937. Pp. 130. R.M.5.80.

THIS little manual is devoted to non-medicinal and non-psychological measures for combating insomnia. A brief review of the physiology and the theories of sleep—with a disapproving note about the psycho-analytic theory—precedes a section on prophylaxis in which the influence of bedroom, bed, bedclothes, and habits upon sound sleep, and the importance of diet and sunshine, are elaborated. The duration and periodicity of sleep and other problems such as the possibility of educating a child to have good sleep habits are briefly examined. In the final section on the treatment of insomnia by "exactly performed prophylaxis," the only methods described are those of hydrotherapy; a brief passage about drugs and another about psychotherapy serve to emphasise the author's preference for water externally in one form or another. The success which he has attained with his "nature cure methods," and the cases he reports, suggest that he has not had much experience of the intractable forms of sleep disturbance sometimes met with in psychiatric practice.

1. Aids to the Treatment of Diseases of Children

Seventh edition. By F. M. B. ALLEN, M.D., M.R.C.P. Lond., Lecturer in Infant Hygiene and Diseases of Children, Queen's University, Belfast; Assistant Physician, Belfast Hospital for Sick Children. London: Baillière, Tindall and Cox. 1937. Pp. 329. 4*s*. 6*d*.

2. Synopsis of Pediatrics

Second edition. By JOHN ZAHORSKY, A.B., M.D., F.A.C.P., Professor of Pediatrics and Director of the Department of Pediatrics, St. Louis University School of Medicine, and Pediatrician-in-Chief to the St. Mary's Group of Hospitals. Assisted by T. S. ZAHORSKY, B.S., M.D., Instructor in Pediatrics at the School, and Assistant Pediatrician to the Group. London: Henry Kimpton. 1937. Pp. 367. 17*s*. 6*d*.

1. Whatever view may be taken of keys, "ghosts," and synopses by the fully fledged physician, they form an important part of the armamentarium of the average student who still has to break through the shell of his examinations. There must be few indeed who have never used one or other of the famous "Aids" series, of which Dr. Allen has supplied one of the more popular volumes. The title is somewhat of a misnomer, as the author considers each disease under the headings of ætiology, symptoms, and diagnosis as well as treatment. In the seventh edition there has been considerable revision of the sections dealing with infant feeding, prematurity, and the specific fevers, whilst asthma and pink disease are included for the first time. The little book is clearly and sensibly written, and despite the wide field covered and the modest size and price of the resulting volume, the author has succeeded in avoiding most of the faults of manner and matter common in books of this kind.

2. Dr. Zahorsky's work, though it contains much useful information and little to which exception could be taken, is not equally successful. By the use of small print he has produced a small, illustrated text-book of pædiatrics which is hardly adequate as a student's primary source of information on pædiatrics, and, on the other hand, is not specially suitable for purposes of rapid revision. The second edition has been extensively revised, a chapter on diseases of the eyes and ears has been added, and several good coloured plates are now included.

Muir's Bacteriological Atlas

Second edition. Atlas enlarged and text rewritten by C. E. VAN ROOYEN, M.D. Edin., Halley Stewart Research Fellow and Lecturer in Bacteriology in the University of Edinburgh. Edinburgh: E. and S. Livingstone. 1937. Pp. 90. 15*s*.

THE late Richard Muir's book has for some years been the only bacteriological atlas in common use in this country. Muir's fame as a technician naturally spread far beyond the walls of the University of Edinburgh where his work was done. He was also an artist in his way and his coloured plates present an almost ideal representation of micro-organisms. Dr. van Rooyen's additional plates are in every way up to Muir's standard and indeed, in places, surpass it. The colour reproduction of the 83 plates is of high quality and considering the cost of such things the price of the book is very reasonable.

The Low Voltage Cathode Ray Tube

and its Applications. By G. PARR, Radio Director, Edison Swan Electric Company. London: Chapman and Hall. 1937. Pp. 177. 10*s*. 6*d*.

THE cathode ray tube is a form of oscillograph which has proved a valuable instrument in the analysis of rapidly altering electrical potentials and currents. It consists essentially of a beam of electrons ejected from a heated filament, concentrated into a fine jet by an electrical field and allowed to fall on a fluorescent screen. The impact produces a luminous spot. The whole instrument is enclosed in an evacuated tube. The pencil of electrons forms a sensitive pointer which can be deflected by electrical and magnetic forces, and, since its inertia is practically zero, the deflections follo v perfectly any variations in these forces however rapid they may be.

Mr. Parr divides the cathode ray tubes into three types according to the voltages applied to them—high, medium, and low. The first class, employing some 60 kv. is not dealt with here, but a detailed and practical description is given of the other instruments which work under various potentials up to 3000 volts. The use of these tubes is rapidly increasing as new applications are continually being found. Any varying quantity, such as sound waves, can be converted into the corresponding electrical variation and analysed on a cathode ray tube, and these instruments have for some time been used in this side of physiological research. Owing to its application

in one method of television, the recent development of the cathode ray tube has been very rapid. The earlier chapters give a very useful and detailed account of how to handle the apparatus—the focusing of the recording spot and its deflection for various purposes.

Our only criticism of this book is that the title is misleading. It suggests a handbook dealing with some particular tube, whereas the subject matter covers all the instruments which are likely to be met with to-day in normal research work.

Manual of Practical Anatomy

By J. ERNEST FRAZER, D.Sc., F.R.C.S., Professor of Anatomy in the University of London; and REGINALD H. ROBBINS, M.A., M.D., Assistant Lecturer and Senior Demonstrator of Anatomy, St. Mary's Hospital Medical School. London: Baillière, Tindall and Cox. 1937. Vol. I, pp. 526; Vol. II, pp. 442. 10*s*. 6*d*. per volume.

THE dissecting-room in a British school of anatomy is traditionally a sort of club where the student spends a good deal of time acquiring conversational arts and incidentally perhaps hoping to acquire technical knowledge by a kind of osmosis. When the preclinical sciences had not much else to offer than a course in dissection of the human body, and physiology, now become so rich and extensive, was forced to eke out its scanty store by teaching histology, it was inevitable that the student should live in the "rooms." Practical manuals of anatomy which fitted into this scheme were used as text-books as well as practical guides. It has now become impossible to continue in this traditional way, and practical anatomy has to be taught by schedules arranged according to a fixed time-table. In most departments special instructions for dissection are issued week by week to its students. Much time is gained by this method, and it is possible to use the time so saved for the study of other aspects of the structure of the body than those of position and topography—aspects even more important, conveying some understanding how the body is made and how it works. In a sense the practical manual in book form belongs to an epoch that is over. But there are still students who find works of this kind do provide them with the necessary amount of information in a period of time that is neither too long nor too short. In this one the text is full and accurate, thus fulfilling the chief criteria of the dissecting manual. The illustrations are not perhaps quite up to the standard of the text, but they show clearly enough what must be looked for at each stage of the work. The long teaching experience of the authors is sufficient guarantee that they have anticipated the difficulties of the average student.

A Textbook of Embryology

Third edition. By HARVEY ERNEST JORDAN, A.M., Ph.D., Professor of Histology and Embryology, University of Virginia; and JAMES ERNEST KINDRED, M.A., Ph.D., Associate Professor of Histology and Embryology at the University. London: D. Appleton-Century Company. 1937. Pp. 613. 25*s*.

THIS text-book is an excellent example of the teaching manual. The text is clear, the illustrations are abundant, the order and logic of its arrangement are manifest, and nothing appropriate to the purpose seems to have been omitted. The usefulness of the work is increased by the inclusion of a laboratory guide and this has been put into a convenient form. It begins with a list of laboratory exercises so arranged that to work through them would entail a complete exploration of the anatomy of the embryo. In addition an illustrated guide is provided to enable the student to find his way through serial sections of the usual laboratory types. Every aspect of embryology is covered, and chapters are included on the recapitulation theory, prenatal and postnatal growth, teratology, and eugenics. Both authors are distinguished biologists, though neither of them belongs to the medical profession. This perhaps may explain the only slip that we have noticed—namely, the use of the term "lochia" in the same sense as "afterbirth."

There is, however, one thing that is lacking in this book. Embryology has now become a great science. Nothing is so dramatic and impressive as the formation of a new organism from a fertilised ovum. The sequence of events by which this is achieved is fundamentally the same for all organisms, and is always the same in the same organism. Since this sequence is so invariable the conclusion cannot be escaped that there must be a causal mechanism behind it. This manual is descriptive in its outlook and does not convey to the student any vivid sense of the dynamic aspect of embryology.

Physiologie de l'innervation rénale

By JEAN HAMBURGER. Paris: Masson et Cie. Pp. 180. Fr.30.

THE kidney has a rich nerve-supply whose function is still in doubt. The different lines of approach of various research workers to this problem are here reviewed and their conclusions criticised. British readers will be astonished to find no reference in the book to the recent work of E. B. Verney, and those interested in special aspects of the subject will find other less obvious omissions. It must be conceded, however, that the various points of view are fairly represented, and the neglect of certain individuals does not impair the main purpose of the book. The author's own experiments are of particular interest. A series of beautiful X ray photographs depict the vascular system of the kidney after injection with Thorotrast, and vasodilatation after nerve section is demonstrated by this means, which is free from many of the objections attending other methods. Briefly, the more complete the denervation, and the nearer to the kidney, the greater the dilatation. There is a suggestion, however, that the nerves in the hilum itself may have the opposite effect. With regard to diuresis, the conclusions of others that denervation has no permanent effect are confirmed, but stimulation of the nerves causes oliguria and albuminuria. The author is unwilling, on the evidence available, to say whether this is a pure vasomotor effect or whether secretory nerves play a part. Perhaps the most interesting experiments deal with orthostatic albuminuria, which can be readily produced in animals. The presence of albuminuria in association with certain nervous lesions is discussed, and experiments are cited which show that denervation of the kidneys prevents the appearance of orthostatic albuminuria in animals which previously exhibited the phenomenon quite readily. The author wisely refrains from drawing any far-reaching conclusions, but stresses the frequent coincidence of vasoconstriction and functional albuminuria. The book is rounded off by a survey of other functional renal troubles met with in clinical practice. It is stimulating, easy to read, and foreshadows results of medical importance

THE LANCET

LONDON: SATURDAY, AUGUST 21, 1937

THE ORGANISATION OF A BLOOD TRANSFUSION SERVICE

A SCHEME for providing a supply of live blood for those who will not without it recover from accident or desperate illness has been described by Prof. W. N. SHAMOV of Kharkov and Prof. S. S. YUDIN of Moscow in the last two issues of THE LANCET. It was born more than ten years ago in Shamov's experimental work on cadaver blood and has been gradually adapted by Yudin to the needs of a surgical clinic. There is little in their description which has not been published in Russian or French papers during this long probationary period. The new fact is the demonstration that the scheme works, and if only on this ground it is worth careful scrutiny. The surgical and accident department of the Sklifosovsky Institute in Moscow serves the needs of a city of some 4 million inhabitants. There are many cases of severe traumatic shock, of copious gastro-duodenal bleeding, of cancer amenable only to extensive excision. The institute now has at its disposal quantities of blood, available day or night for immediate use, sufficient to meet all these needs. The stored blood is sterile; the risk of conveying syphilis has been excluded; and provided the usual group compatibility is observed there is little fear of any biological reaction. Furthermore the blood is not only a suitable colloidal fluid; it has retained completely its rôle as an oxygen carrier. All this has been achieved, as every one has been dramatically told, by the use of corpse blood, or, as it might more gently be expressed, with the coöperation of patients who have passed beyond reach of help for themselves. There is a constant stream to the institute of such unsaved lives whose vital fluid is still intact and an average of two litres of blood can be drawn from the jugular vein through a small incision in the neck. At first some objection was taken to this vicarious use of human blood. To the primitive mind the blood is the bearer of mystic qualities, and there is in Russia an instinctive fear of giving away so valuable a part of the organism, coupled, Shamov suggests, with an equally instinctive reluctance to disturb the repose of the dead. These have been met by the counter-suggestion that the relations of the dead person should feel satisfaction at rendering so noble a service to fellow sufferers, and the medico-legal difficulties were solved after the Kharkov congress of 1930 had secured the assent of surgeons generally to the principle. The papers which we published tell the story of how during the last ten years every hindrance has not only been met but regarded as a stepping-stone to further endeavour. Whether imitable elsewhere or not it is a splendid object-lesson.

Before turning to the absorbing question of imitation it would be well to consider briefly the special claims made in Russia for the use of cadaver blood as a restorative in preference to blood from the living, even if this were equally available. In the second paragraph of his article Shamov asks a question whose solution has captured his imagination and informed his whole inquiry. It is this: can a defect in a living body be remedied by the transplantation of tissue from the dead, already doomed to perish? More than 20 years since PEYTON ROUS and J. R. TURNER [1] showed that it was possible to preserve human red blood-cells alive for several weeks in a solution of dextrose and citrate at ice-box temperature, and that the results of transfusion with preserved blood were as striking as those seen after transfusion with blood freshly drawn. After disposing of the bogy of harmful cadaveric toxins Shamov has come to attribute vital, almost it seems mystic, properties to the surviving blood of dead donors, which has in his hands showed qualities transcending that from living donors—namely, a less hostile reaction and a better stimulus to new blood formation. And with this Yudin's clinical experience has now led him to agree. On a more humdrum level it is obvious that it is easier to exclude evidence of syphilis or other disease in the leisurely examination of a dead donor, thus removing the difficulty of a Wassermann reaction while you wait. But there is another advantage which has emerged from the Russian work and may be fundamental. The blood drawn from a corpse after sudden death in cases where there has been no prolonged agonal disturbance first coagulates and then undergoes a liquefaction owing to the gradual disappearance of fibrinogen. It is known that blood effused into large body cavities may remain fluid for a long time and R. G. MACFARLANE has recently found [2] that fibrinolysis may occur in blood withdrawn after surgical operation. It is amazing that post-mortem liquefaction should for so long have failed to attract attention; its significance in regard to intravascular clotting remains to be seen. The work of Skundina and Russakov, quoted by Yudin, suggests that the liquefaction of the coagulum formed immediately on withdrawal of the blood is not associated with actual digestive breakdown of the fibrin. This spontaneous liquefaction means that cadaver blood requires no addition of anticoagulant and to this freedom of the transfused blood from citrate is attributed the reduction in the number of reactions. In this country large infusions of citrated blood are constantly being given by the Marriott-Kekwick continuous drip process. Yudin remarks that the effect of large quantities of sodium citrate in the circulation is quite unknown. Experience here already indicates that they do no immediate harm.

[1] *J. exp. Med.* 1916, **23**, 219.
[2] *Lancet*, 1937, **1**, 10.

What may be the ultimate effect of anticoagulants on stored blood we do not know.

So much for the claims made for the Russian scheme, the success of which in situ is impressive. Can and should it be imitated? The use of blood from dead bodies seems to be repugnant to the British mind and the same feeling has been evinced in Canada and America. It has been overcome in Russia where in this respect reason has triumphed over instinct. If the voice of medicine was certain it would hardly be less impressive here. It is partly a question of nomenclature. No one would like to think of being revived by corpse blood, but would he feel any hesitation at a supravital infusion? And the appeal of man to help man is a growing factor in current psychology. If popular repugnance was overcome there would remain the obstacle of the law which constitutes the coroner the guardian of accidental death. For the moment the Russian scheme should be a stimulus to the organisation in this country of voluntary donors. The creation of a national service on a voluntary basis, with branches in all provincial towns, is now under discussion by the British Red Cross Society, whose Voluntary Blood Donors Association already provides a highly efficient foundation for such a service. With the growing knowledge of the best means of preserving blood the establishment of depôts should be increasingly possible. The contribution to a depôt of a pint of blood once or twice yearly at the donor's convenience might lack the romance and excitement which attaches to the sudden call and the hurried journey to hospital; it would also lack its inconvenience. Whether the prospect of contributing to an impersonal pool rather than to an individual sufferer would dry up the springs of altruism remains to be seen; if it did, other sources could be made available. The Cook County Hospital, Chicago, has established a blood bank.[3] To this all members of the staff make contribution of blood from patients under their care in the wards; it may be taken from the subjects of congestive cardiac states who are better without it, or from others who can well spare it. On this bank the staff are at liberty to draw as occasion demands, paying in the equivalent at the next opportunity. It is unfortunate that the peculiar organisation of the practice of medicine in this country places most of the blood transfusion work in the hands of medical men attached on a part-time basis to the hospitals which they serve, and who have neither the time, the assistance, nor the laboratory equipment to attempt to solve this problem.

THE NATIONAL CRIME-SHEET

THE exemplary behaviour of the feminine sex is once more the salient feature of the annual Criminal Statistics. The report for 1935 (Cmd. 5520. H.M. Stationery Office. 3*s*. 6*d*.) shows that while over 60,000 males were found guilty of indictable offences, the total for females was much less than 9000. When the figures are divided into age-groups another striking fact emerges. More than half the offences committed by males are by boys or youths under 21; 39 per cent. indeed are committed by boys under 17. The women, when they are bad, grow worse as they grow older; only 17 per cent. of their offences are committed under the age of 17; in the age-group from 21 to 30 the percentage for women is almost identical with that for men; but the group aged 30 and over is responsible for 47 per cent. of indictable offences among women against only 26 per cent. among men. The inventor of the motor-car seems indirectly to have caused most of the crime in England. Out of the total number of offenders of all kinds traffic offences accounted for 57 per cent. in 1935. Only 9 per cent. were real crimes, that is to say, the indictable offences which go to assizes and quarter sessions. Three-quarters of these real crimes were larceny, 20 per cent. committed by children under 14 and 51 per cent. by persons under 21. Traffic offences jumped up by nearly 100,000; it is easy to realise the extra strain they impose upon our police forces. Drunkenness, which declined from 1920 to 1932, is showing some increase in recent years. Prostitution offences are up by over 50 per cent.; the figure for 1935 is over 2½ times the figure for 1931. A strange element in our annual crime-sheet is the recurrence of nearly 27,000 offences of Sunday trading in those few districts where it is the practice to levy fines on shopkeepers for conduct which is presumably felt to be *malum quia prohibitum* rather than *malum in se*. The shopkeeper prefers to keep his premises open and pay his fine, making the best (or the worst) of both worlds; the locality is not ashamed to put a premium on unlawfulness, but draws its royalties regularly in relief of local expenditure. Foreigners could hardly find a better instance of the English conservatism which hesitates to repeal Lord's Day Observance Acts and the English ability to compromise with conscience. To turn to something more honestly criminal, the figures of murder remain as stable as ever, no matter how population varies. About 100 persons, aged one year or over, are known to the police to have been murdered in the year. In half these cases in 1935 the murderer or suspect committed suicide. In 2 cases, involving 2 victims (one of whom died after an illegal operation), no arrest was made. Forty-seven persons were arrested on charges of murder and 8 of them were hanged; 6 were found insane on arraignment, 14 obtained the ridiculously expressed verdict "guilty but insane," 1 was certified insane after conviction and was removed to Broadmoor. It is a useful illustration of the difference between the legal and the medical standards of insanity; the law has insisted on getting its verdict of "guilty" against many men whom alienists would regard as of deranged mind. The cost to the community of the existence of mad murderers is shown by the statistics of criminal lunacy. There were 413 of them in asylums at the end of 1935; 106 had been detained for twenty years and over.

There is a grand total of 759,423 persons found guilty in 1935 of offences of all kinds. What

[3] Fantus, B., *J. Amer. med. Ass.* July 10th, 1937, p. 128.

happens to them? Over 99 per cent. were dealt with by the magistrates, less than 1 per cent. went before a jury. Dismissal of the case after the charge has been proved, binding over or placing under a probation officer accounted for 16 per cent.; 80 per cent. were fined; only 3 per cent. were sent to prison, penal servitude, or Borstal. In its preface to these annual statistics the Home Office gives particular emphasis this year to corporal punishment in view of the Home Secretary's decision to appoint a committee to examine the question. We are shown the figures since 1904 of persons convicted of robbery, for instance, and sentenced to corporal punishment. This type of sentence is more frequent since 1920 than in pre-war years. The analysis of the orders made by juvenile courts for administering the birch rod shows that the total of 218 comes from quite a small number of courts. None of the metropolitan juvenile courts or the juvenile courts in big towns like Birmingham, Liverpool, Sheffield, Leeds, Bristol, Cardiff, Portsmouth, or Plymouth, ordered the birch, whereas small towns like Windsor (7 orders) and Winchester (5 orders) retain a faith in the rod which it is tempting to ascribe to famous local traditions. In the past 33 years, the report tells us, 47 men have been sentenced to corporal punishment for indecent exposure; medical science, if its exponents were encouraged to investigate such cases, might well show some better method of dealing with exhibitionism.

It is tempting to pick out the singular variations displayed by magistrates in different parts of the country. Why do the Southampton justices place only 9 per cent. of adult offenders under probation when the percentage for Portsmouth is 34? Why is the corresponding percentage for Blackpool under 10 when at Southend it is over 37? Why, in the counties, is it as high as 44 in Hertfordshire and as low as 8 in Devon? Similar variations are visible in the tables about coroners. The coroner for South Buckinghamshire directs or requests post-mortem examinations in 60 cases and is able to dispense with an inquest in 42 of these; the Crediton district coroner with a higher total of inquests has a post-mortem examination in only 8. Is the anomaly due to the lack of local facilities? These post-mortem figures reveal a further diversity. They are grouped under "Inquest cases" and "Non-inquest cases." In Bristol the coroner directs or requests 372 post-mortem examinations in inquest cases against 26 in non-inquest cases; conversely in Liverpool the respective figures are 90 to 335. Fewer autopsies were asked for by coroners in 1935 than in 1934, though the total of inquests was slightly larger. The number of inquests held by the coroner without the assistance of a jury (rather more than a quarter of the whole) continues to rise. Lastly, it is worth noting that the number of inquisitions quashed or amended by order of the High Court in 1935 was no more than one out of over 67,000. Can the reformers deduce from this any overwhelming need to alter the constitution and practice of the coroner's court or to bar the appointment of men with medical qualifications?

ÆTIOLOGY OF CANCER OF THE BREAST

THE investigation of cancer by genetic methods has reached an interesting stage. The official publication of the International Union against Cancer [1] contains no less than three reviews on this subject, one by Prof. R. KORTEWEG of Amsterdam, one by Dr. L. KREYBERG of Oslo, and a third by Prof. LEO LOEB of St. Louis. A review on the same subject by Mr. A. P. GORER appears elsewhere in this issue. What has happened in this field of cancer research to stimulate all this activity? The study of cancer by the methods of genetics had disclosed the remarkable fact that by inbreeding it is possible to produce genetically pure strains of mice in which the mamma will exhibit the development of malignancy in either a uniformly high or a uniformly low percentage of female animals. Until recently this was advanced as an argument to prove that the ætiology of cancer generally was essentially a problem of genetics and could be explained along mendelian lines. This view has never found acceptance by experimental pathologists. On general grounds they have been unable to look upon the highly complex group of biological phenomena, which for the sake of convenience are grouped together under the term "cancer," as if it was homologous to such comparatively simple biological phenomena as body size or coat-colour. Furthermore, in using a different tissue—the skin—as their test object, they found that although the skin of the mouse is very susceptible to the development of malignancy it does not show a high incidence of spontaneous skin tumours and that it was not possible by inbreeding to obtain a genetically pure strain of mice with a uniformly high incidence of spontaneous skin cancer. The study of carcinogenesis in the skin showed that the development of malignancy in that tissue depends on two main factors: the presence of a carcinogenic substance applied from without and the factor of susceptibility of the skin to that substance. The further study of the development of mammary cancer in genetically pure strains has gradually led to the same conclusion. Thus W. S. MURRAY [2] found several years ago if the ovaries of mice of a pure strain with a high incidence of mammary cancer in the females were transplanted into the males of the same strain that mammary cancer could be made to develop in the males. A. LACASSAGNE [3] performed the crucial experiment of producing mammary cancer in the males of such a strain by the prolonged administration of the ovarian hormone—œstrone. He demonstrated further, that œstrone will produce mammary cancer more readily in males belonging to a strain with a high incidence of mammary cancer in the females than in those belonging to strains with a low incidence, and that œstrone will fail to elicit mammary cancer in the males of a pure strain in which no spontaneous cancer of the mamma ever develops in the females. The conclusion that two factors—carcino-

[1] *Acta*, 1937, **2**, 136, 146, 148.
[2] *J. Cancer Res.* 1928, **12**, 18.
[3] *C.R. Soc. Biol. Paris*, 1934, **115**, 937.

genic substance and susceptibility—are essential for the development of mammary cancer in pure strains was thus established as clearly as it had been for skin cancer in mixed strains. The apparent difference between the ætiology of skin and mammary cancer finds an explanation in the fact that in mammary cancer both factors reside within the organism, while for the skin only the factor of susceptibility resides within the organism and the carcinogenic substance has an external origin. The result of inbreeding is to accentuate only the factor of susceptibility or insusceptibility as the case may be. As Mr. GORER points out, an explanation along mendelian lines may be applicable to the inheritance of the factor of susceptibility but not to the more complex phenomenon—the incidence of cancer of the mamma. The term susceptibility to mammary cancer is a vague—a deliberately vague—term, and it is by no means established that the factor of susceptibility resides entirely within the cells of the mamma. CRAMER and HORNING [4] found that the adrenals of mice from a genetically pure strain with a high incidence of mammary cancer undergo spontaneously a specific process of degeneration preceding the appearance of cancer of the mamma, and that the same process of degeneration can be induced in mice of mixed strains, in which it does not appear spontaneously, by the prolonged administration of œstrone.

Another new problem is introduced by the remarkable observation of J. J. BITTNER, referred to by Mr. GORER, that the fostering of the newly born females from a high cancer strain by mice from a low cancer strain greatly reduces the incidence of mammary cancer. It must be realised that these animals belong to a strain which, according to genetic conceptions, is still genetically pure and ought to have a high incidence of mammary cancer. It follows that in genetically pure strains of mice "some influence," as BITTNER calls it, is transmitted through the mother's milk, which is of prime importance in determining the incidence of breast cancer. Here again an explanation along genetic lines is not easy to imagine. What is the part played by this factor, transmitted by the mother's milk, in the ætiology of breast cancer? Is it concerned with the susceptibility factor or with the carcinogenic factor? And what is the nature of this "influence"? Is it inanimate—a chemical substance, or animate—a virus? The ingenuity with which cancer research workers are unravelling these intricate conditions makes it likely that we shall not have to wait long for an answer to these exciting problems. They may have an important application in the prophylaxis of breast cancer in women. The evidence presented by CRAMER in a recent paper on the ætiology of cancer of the mamma in the mouse and in man [5] shows that in the human subject also the mamma is an organ for which the familial incidence of cancer is exceptionally high.

[4] *J. Path. Bact.* 1937, **84**, 633.

[5] *Amer. J. Cancer*, 1937, **30**, 318.

ANNOTATIONS

THE ACCURACY OF THE MEDICAL DIRECTORY

UP to the year 1920 it was the practice of the Medical Directory to affix an asterisk sign to the names of those who had not returned the annual circular and whose entry therefore might be imperfect or misleading. In that year an alteration in paragraphing crowded out the asterisks, and in recording this omission we expressed the hope that it would not lead to any less diligence, on the part of the publisher or on the part of those who supply the information, in keeping up the standard of a work of reference whose value depends on being up to date. The contributors indeed may take honest pride in the result of their collaboration, for the directory is unique of its kind as anyone will discover at once if he looks for the same thing in other countries; and although it has no legal value as evidence, the directory is nevertheless freely used by public bodies for supplementing the official but scanty record of the Medical Register. Time has gone by and the task of editing the Medical Directory has not become more easy; hundreds of circulars were not returned, and two years ago we came to the rescue by printing the names of those who had not communicated their present address to its editor. The list was surprisingly long and its length explained among other things how it is that so many members of the medical profession get their names removed from the Medical Register owing to failure to notify their whereabouts to the Registrar of the General Medical Council. The effort of the Medical Directory if successful would obviously have been of real benefit to those who had inadvertently run the risk of erasure. The reminder was in fact seen by many of them or brought to their notice by their friends. Rather disappointingly however the names of uncommunicated addresses which appeared in the following year included a number of those who had already been warned. No further reminder will be issued but we have been asked to appeal to members of the medical profession who have not already communicated their present address to the directory to do so now and to confirm or correct the personal details. Failing that, the words "Address uncommunicated" will appear in lieu of an address in the Medical Directory for 1938. This is not a reprisal; it is no more than fair to warn readers of possible disappointment.

MIDWIFERY IN RURAL AREAS

THE Associated Country Women of the World have been sufficiently interested in the problems of rural midwifery to make an inquiry from representatives in many part of the world and to issue a report.[1] Lady Eleanor Cole, who contributes a foreword to this report, remarks that she has selected from the replies to a questionnaire those facts that seem peculiar to the country in question or that have been unmentioned by other countries, and the result is an interesting and rather stimulating survey of what is lacking to women faced with the hazards of childbirth in inaccessible districts, with hints on directions

[1] Special supplement to the *Countrywoman*, August, 1937, 3*d*.

in which the need might be met. Dr. Esther Carling, in a summary of the replies, says they showed straight away the presence of two streams of thought: (1) Should these be centred round the home or the hospital? (2) Should they focus on the well-trained midwife or on the medical practitioner? It is evident, she remarks, that established tradition and local circumstances must first determine the focus of endeavour. In New York State only 2 per cent. of deliveries take place outside hospitals; in France the avowed aim is to make it possible for every child to be born safely at home. In America there is hardly any organised midwifery by midwives; in France the sage-femme has never been replaced by the medical practitioner in domestic midwifery. Making these allowances, Mrs. Carling asks whether it should not be possible to agree upon two foundation principles: (1) team-work everywhere, but team-work based upon (2) midwives for midwifery. She recalls how in this country one of the blackest spots of high maternal mortality was changed "not to grey but straight to white" by a concerted drive. No one doubts in this case the relation of cause and effect. What is the doubt in some minds is that although it may be possible in some areas at some times to keep efficiency up to peak level, it can hardly be possible for this to happen at all times and in all areas. Perfect team-work may cover up individual deficiencies, but in the long run the result must depend on the training of the several members of the team. There are, Mrs. Carling thinks, indications all over the world that even in quarters where hospital care is desired the midwife shall be at the heart of the service; and the report is enlightening in its account of the varied time and method of training of midwives in various countries. In New Zealand, with the consent of the attending doctor, the midwife is allowed to administer chloroform to the obstetrical degree; elsewhere, it is suggested, her inability to relieve the pains of labour has often tilted the scale against the employment of the midwife. But the determination in this country to organise relief from pain will, Mrs. Carling is sure, not remain an isolated endeavour. The approval given by the Central Midwives Board to the administration of gas and air by midwives should within a few years bring the possibility of obtaining relief within the reach of parturient women everywhere.

SHOULD THE ECZEMATOUS WASH?

THE principle that should govern the treatment of an eczematous skin is to put it at rest and not irritate it by antiseptic applications or by the constant effort, born of surgical training, to "clean up the part." The less the interference with the skin by patient or doctor, the better for the eczema. It is probably wrong repeatedly to clean pastes off the skin for fresh application since the injury occasioned by the removal cancels the virtue of the treatment. Paste applications should be left undisturbed and healing will take place beneath them. Goldman [1] has recently investigated the reaction of the skins of infants and children to soaps by patch-test methods, using small bits of soap, 10 per cent. and 5 per cent. solutions, and by repeated swabbings. In testing 127 children against seven common soaps he found no reaction to repeated swabbings. Mild reactions were obtained to patch tests, more commonly in children than in new-born infants and rather more noticeably to a soap containing cresol than to the other soaps tested. Balyeat [2] had also observed this fact. In a previous investigation Goldman [3] had found that pure coconut oil soaps provoked more reactions than others.

While the damaging effects of soap and water may be due to alkaline irritation, certain persons react to soap because they are hypersensitive to one or more ingredients. Hazen [4] found 8 such patients in a series of 127 and all investigators agree that those subject to contact dermatitis are more liable than normal subjects to react to soaps. This may well be a cause of persistence or relapse of dermatitis. Most authorities would probably agree that the use of soap is undesirable in the presence of eczema; some forbid even plain baths or insist upon the addition of bran or oatmeal as a softening agent. Others, perhaps on theoretical grounds, regard the use of an isotonic saline solution for cleansing purposes not only harmless but beneficial and desirable. Actually some patients and some conditions may be harmed and some helped by the use of water. Probably much depends upon the common sense and intelligence of the patient in using baths. The even pressure of a warm water bath is soothing; a very cold or very hot bath is ultimately irritating in spite of any immediate relief to itching. It is desirable to lie in the bath and not to wash the skin; to blot dry subsequently with a soft warm towel without rubbing. The temptation to scrub the skin with a rough towel on leaving the water is one to be resisted and the desire to do this will pass. The use of the bath is obviously only suited to certain temperaments and demands a degree of intelligent coöperation between patient and practitioner.

ILLICIT TRAFFIC IN NARCOTIC DRUGS

THE advisory committee of the League of Nations on traffic in opium and dangerous drugs has re-elected Dr. Chodzko of Poland as chairman, Mr. Delgorge of the Netherlands as vice-chairman, and Major Coles of the United Kingdom as rapporteur. The committee call attention to the fact that the absence of drug-addiction within a country does not necessarily imply that clandestine manufacture leading to illicit traffic can be excluded. They deplore the fact that the smuggling of opium, and to a greater extent of manufactured drugs, by certain foreign nationals in China is paralysing the laudable efforts of the Chinese Government to deal drastically with the drug situation. The coöperation of Japan is invoked to arrest the "appalling" state of things in the provinces now under Japanese influence. It was reported to the committee that "from Dairen thousands of letters containing drugs were posted to the United States of America, Egypt, and elsewhere." A disquieting statement appears in the report of a subcommittee on "seizures" in regard to the development of a new type of market for prepared opium in Canada. It is alleged that the use of this drug, formerly limited to smoking, has now extended among occidentals on the Pacific coast, to include hypodermic (usually intravenous) injection. This habit began to be encountered shortly after measures of local control had rendered morphine, heroin, and codeine impossible or at least very difficult to obtain. The habit brings with it the serious risk of very severe abscesses from the injection of the opium. This development naturally causes Canadian and American narcotics administrations to view with

[1] Goldman, L., *J. Amer. med. Ass.* 1937, **108**, 1317.

[2] Balyeat, R. M., *Northw. med. J., Kimberley, Idaho*, 1935, **34**, 12.

[3] Goldman, L., *Univ. Cincinn. med. Bull.* 1935, **7**, 90.

[4] Hazen, H. H., *Arch. Derm. Syph.* 1928, **18**, 121.

special concern the recent large seizures of smoking-opium destined for the illicit traffic in North America. The advisory committee is now concentrating its attention on three important questions—namely, "the situation in the Far East, the clandestine manufacture of narcotic drugs, and the preparation for a conference on the limitation and control of the cultivation of the opium poppy." This last topic, which has been discussed for years without any drastic outcome, is surely fundamental to the other two and to the whole problem of international control of drugs of addiction.

A CHANGE OF POLICY

ALL those who have the care of tuberculous patients should be aware of a recent change of policy in the application of the Queen Alexandra Sanatorium Fund. It was the wish of the late Lord Balfour of Burleigh that the climatic advantages which he knew so well in the Davos valley should be at the disposal of persons of small means, and it was his personal influence and enthusiasm that brought into being the English Sanatorium which at long last took the place of the old British Home. This sanatorium was opened in 1909 and closed in October, 1914, after five years of useful service. It was never reopened; the difficulties of transit and exchange were too great, and in 1922 the building and all that it contained was sold for use as a Swiss popular sanatorium. The proceeds were then used in the form of grants to enable patients to go to Davos or to prolong their stay there when they would not otherwise be able to do so. But during these years the treatment of pulmonary tuberculosis has been developing rapidly and there are now in England sanatoria with a technical equipment as good as any in Switzerland. At its recent annual meeting, over which the present Lord Balfour presided, the medical members of the Fund council firmly expressed their opinion that treatment and régime are more important than climate, and it was decided then and there to ask the Charity Commissioners so to alter the original constitution of the Fund as to allow the grant to be used for treatment in sanatoriums at home. This decision does not preclude a grant for alpine treatment in any case recommended for it by the Fund's medical advisers, nor is it proposed to discontinue the treatment of children in Switzerland, which has been so happy a feature of the Fund's recent activities.

POISONOUS UMBELLIFERS

FOUR poisonous members of the umbelliferæ family are common in the British Isles and have frequently been the cause of death in cattle and other domestic animals and, more rarely, in human beings who sometimes mistake them for parsley or parsnip. Of these four the spotted hemlock and fool's parsley are found in hedges and waste places generally, whereas the water hemlock and the water dropwort favour marshy ground and the banks of ditches. Spotted hemlock, *Conium maculatum*, owes its poisonous properties to the alkaloid coniine which acts upon motor nerve-endings and causes death by paralysis of the respiratory apparatus. The symptoms of poisoning by this plant are first a burning pain in the mouth and vomiting from local irritation, followed by increasing weakness of the legs and dyspnœa with cyanosis. Convulsions sometimes occur but are unusual. It was from spotted hemlock that the Greeks probably prepared their official poison for the use of those who had been condemned to compulsory suicide, and the symptoms which Plato describes as preceding the death of Socrates certainly resemble those of coniine poisoning. The active principles of the other three poisonous umbellifers appear to be similar in action to picrotoxin and produce cerebral irritation followed by paralysis. McGrath has recorded [1] a typical fatal case of poisoning by water dropwort, *Œnanthe crocata*, which recently occurred in southern Ireland. A child aged nine dug up and ate roots which she found growing on the bank of a river in co. Kerry. She vomited and appeared to be very ill almost immediately, and within a quarter of an hour she collapsed and rapidly became unconscious. She then began to have severe general convulsions at short intervals, and showed signs of respiratory failure for which artificial respiration had to be given. Although her breathing later improved the convulsions continued and could be checked only for a time by the administration of chloroform. She became progressively weaker and died three hours after she had eaten the roots. Post-mortem examination showed little that was abnormal. The mucous membrane of the pharynx, œsophagus, and stomach was slightly injected, and there was some congestion of the lungs and on the surface of the brain. An attempt was made to isolate the toxic substance from the stomach contents but the oily fluid which was ultimately obtained had no effect upon a guinea-pig into which it was injected. It is clear, however, that the active principle of water dropwort, which has been named œnanthotoxin, is a potent one. Further study might show that it has some therapeutic uses.

MILK CURD AND INFANT FEEDING

WHILE the present general interest in various aspects of cow's milk as a food and as a commodity has never been exceeded, the question of the best form of its administration to infants has not received much attention recently. There is still much difference of opinion in this country among pædiatric experts, all of whom would, however, agree that with differing formulas they have the same object in mind—namely, to give the baby who must be fed in an unnatural manner the most satisfactory dietetic mixture. While experts disagree the practitioner remains fretted by such problems as when (and when not) to use sodium citrate; what is humanised milk; and are Truby King nurses always right? The Council of Foods of the American Medical Association has recently attempted, by authoritative surveys,[2] to help those who are confused. One concerns the question of curd digestibility, this being the part of cow's milk which is most likely to disturb the human baby's stomach. Tests on what is termed "curd tension" have been carried out over a number of years, the method being to coagulate milk by a solution of pepsin and measure the force required to pull or push a knife blade through the resultant curd. With raw milk this tension is usually high, although there are many variations between the products of different cows. The modification of the curd, which means in effect reducing the curd tension, can be achieved in many ways, of which boiling, dilution, and the addition of acids or alkalis, in that order, appear to be the most effective measures. Similar conclusions were reached by H. L. Wallace [3] in an address delivered to the Edinburgh Obstetrical Society earlier this year. Wallace had also conducted certain tests on milk which was clotted by the addition of rennin; he found that after dilution by water and boiling the size and toughness

[1] McGrath, J., *Irish J. med. Sci.* July, 1937, p. 309.
J. Amer. med. Ass. 1937, **108**, 2040, 2122.
[3] *Lancet*, July 3rd, 1937, p. 22.

of the milk curd were so reduced that there was no advantage in adding sodium citrate. The addition of partially dextrinised starchy foods to milk did not in these Edinburgh experiments affect the size and consistency of the clots. Dried milk prepared by the roller process produced a fine precipitate, but in the specimens dried by the spray process that were tested in Edinburgh there was some clotting, although the individual curds were comparatively small and soft. The application of such experiments to everyday problems of infant feeding is carried a stage further in the American reviews by a survey of certain clinical experiments. These show that in general milk with a low curd tension is less likely to be delayed in the stomach and such digestion as takes place in the stomach is more quickly accomplished when the curd is soft. On the whole the best digestion appeared to be obtained with ordinary boiled milk, and there seemed no obvious advantages, as far as clinical observations went, in making special additions of acids and alkalis or patent foods. This conclusion is in accord with that reached by Wallace—namely, that fresh cow's milk boiled, diluted with water, and containing added sugar and cream in the required amounts is a good programme, although from other considerations Wallace concludes that a good variety of dried milk is probably the best available substitute for human milk. There is thus agreement on one aspect of infant feeding. The next step is to settle the important question of the degree to which cow's milk should be diluted for infants.

A CENTURY OF CORNEAL TRANSPLANTATION

A REMINDER of the fluctuations between popularity and oblivion to which new methods of treatment are liable before they are finally either adopted or abandoned is to be found in this week's extract on corneal transplantation (see p. 474) from THE LANCET of 100 years ago. Ophthalmology can supply at least two other examples of methods which after a series of ups and downs have at last won through. Cautery puncture was used empirically with some success nearly a century before Gonin, while contact lenses were first made in 1850 though they have only been worked out effectively during the last three or four years. The attempts to devise a way of transplanting a cornea to relieve blindness deemed incurable, described by Dr. Bigger in 1837, were the outcome of some measure of success in treating a blind gazelle. There have been many revivals since the natural urge to substitute a transparent tissue for an opaque one which stimulated this experiment on 18 rabbits, of which no less than 16 are said to have recovered some degree of vision. But only quite recently has corneal transplantation been regarded as really practicable, offering if properly applied good prospect of restoring some measure of sight. At the present time the method is engrossing the attention of many workers anxious to improve a technique which is still far from perfect though it is maintained that of operations on "suitable cases" about half are successful according to criteria laid down by Mr. Tudor Thomas.[1]

The feasibility of transplantation of the cornea was naturally dependent in large measure on the state of surgery in general. Good results could hardly have been expected in pre-antiseptic or even pre-aseptic days; it is interesting to read that Dr. Bigger made the observation, though he was not in a position to appreciate its significance, that by the local application of a weak solution of sublimate his results would be greatly improved. Not only asepsis but modern researches into tissue culture, tissue viability, and serological reactions have helped in the evolution of a practical method of performing this delicate operation. Even 100 years after Dr. Bigger's first experiments there is still not only controversy on points of procedure, but indeed little unity of opinion beyond a general concurrence that the operation is practicable, and that the results are roughly those attained by Dr. Bigger—namely, union of a very high proportion of the grafts, with involvement of the iris and partial opacification of the graft as the commonest complications. Rabbits are still mostly used as the subject of experiments, though it is possible that some mammal in which the ratio of the area of sclera to the area of cornea approximates more nearly to the human type would yield better results. The notable successes of Tudor Thomas on rabbits show that even in the more difficult types of eye perfectly transparent grafts can be obtained. Workers with human material continue to get results which are encouraging, if not as spectacular as the popular press would have us believe. The operation will certainly restore in a high percentage of cases sufficient sight to enable a patient whose vision may have been reduced to perception of light to get about unaided and in some cases even to read again. The results appear to vary between 3/60 and 6/18 for distant vision; but this must of course depend not only on the transparency of the cornea but also on the functional efficiency of the other parts of the eye.

It is obvious that with further improvement in the technique the operation will come to have a wider and wider field. Filatov has pointed out that of the 234,000 persons in the U.S.S.R. known to be blind in 1932, 43 per cent. had lost their sight from opacities of the cornea, of which a large number are suitable for operation. There is no doubt therefore of the need, and this brings us to the two main problems of the present time, namely, the supply of grafts and the best method of inserting them. Supply is difficult since only human material is suitable. Elschnig, Imre, Tudor Thomas, Ryeroft, and most other workers at the present time use corneas from eyes excised for injury or for disease (other than infective) of the back of the bulb. The supply of such eyes is naturally both limited in quantity and incalculable in time and place of opportunity so that of the scanty material available much must unavoidably be wasted. Filatov[2] has performed the operation in 95 cases using human material taken from the eyes of cadavers, often many hours after death, and preserved at low temperatures for periods up to 56 hours. The results afford proof beyond doubt that such grafts will unite quite as well as those taken from freshly excised living eyes. There was not a single case of necrosis of the graft. Further figures are perhaps desirable in order to assess the final transparency of the grafts, which may well depend on operative technique and after-treatment quite as much as on the source of the material.

The question of the type of operation is still to be decided. The main uncertainties concern the best size of the graft, the method of keeping it in position (sutures or conjunctival flaps or contact glasses and how applied), and the use of various solutions (e.g., oils, Ringer's solution, weak antiseptics) in the process. All that can be said at present is that though each worker is apt to advocate his own method with enthusiasm, the results obtained appear to be fairly uniform. The difficulty of assessing and

[1] Thomas, J. W. Tudor, *Brit. med. J.* 1937, **1**, 114.

[2] Filatov, V. P., *Lancet*, 1937, **1**, 1395.

comparing them accurately could be removed if workers would classify them according to a common plan, for example that outlined by Tudor Thomas,[1] and would report not only the successful cases but the proportion of successes to attempts. This is the more desirable because corneal transplanting is beginning to yield encouraging results, and Filatov's demonstration that cadaver eyes can be used will doubtless extend its scope. Further experiment is however needed since though there is now no difficulty in getting a graft to take, it is still impossible to ensure that it will remain clear.

LORD NUFFIELD AS APOTHECARY

ON Tuesday afternoon Dr. A. P. Gibbons, as his last official act of mastership, conferred the honorary freedom of the Society of Apothecaries of London upon Lord Nuffield, the certificate being handed to him in a casket of cedarwood. Dr. E. W. Ainley Walker, who presented Lord Nuffield to the Master, spoke of the time and thought he had given to the alleviation of suffering and the improvement of the health and well-being of the less favoured of his fellow-countrymen. "We, of the Art and Mystery of the Apothecaries of London," said Dr. Walker, "regarding ourselves as the representatives of the general practitioner and family doctor, on whom the responsibility for the health of the people ultimately rests, . . . have offered him the highest distinction it is in our power to bestow." And at the court dinner on the same evening, when Lord Nuffield replied to the toast of "Our new Honorary Freeman," he said he proposed, as far as in him lay, to continue to help medicine and surgery, and, he added, to help the teaching that goes to bring about their progress. There is something heartening in the thought of Lord Nuffield as an apothecary. For three centuries and more the apothecary has been the prototype of the general practitioner. Physicians and surgeons have had their charters, but time and again the apothecaries have gained praise for their charity. And the new freeman is helping to level out what Prof. John Hilton has called our social and economic pyramid. A few days ago was announced his gift of £50,000 to Pembroke College, Oxford, to enable poor and deserving students to enter the college, special regard being had to the needs of those who propose to study medicine. In Tuesday's *Times* Prof. Hilton restated the facts that there is much fine talent among sons of working-class folk, and that a large proportion of these highly talented stand no chance of educational advancement, despite existing educational ladders. It is no use, he said, providing more ladders to the top unless the top is flattened. These facts have been there all the time for anyone to take up, but they have made no stir. His own angry reaction to them, although he writes regretting his anger, has now made a stir. Lord Nuffield is helping to put the matter right as far as medicine is concerned.

STATIC ELECTRICITY IN OPERATING THEATRES

THE explosion of anæsthetic mixtures is a risk that still awaits complete solution, and, at the request of the joint anæsthetics committee of the Medical Research Council and the Royal Society of Medicine, the National Physical Laboratory has been giving attention to the electrification of equipment used in operating theatres. The director of this laboratory invited [1] superintendents of hospitals to ascertain from operating theatre staffs their experience of sparking from the movement of blankets, mattresses, and the like, and in this and other ways a good deal of corroborative information has reached the laboratory from hospital superintendents. The work has now been completed and the results show that it is frequently possible by the friction of such coverings to generate electricity of an intensity sufficient to ignite or discharge a mixture of ether and oxygen. The accumulation of an electric charge depends upon some part of the equipment being insulated, and the rubber wheels of trolley couches, tables, chairs, anæsthetic apparatus, and operating tables may provide this insulation. A simple method of preventing its accumulation is to earth the metallic parts of the equipment by a few inches of light chain trailing on the floor. The granolithic type of flooring generally found in operating theatres, though having a high electrical resistance, has nevertheless sufficient conductivity to dissipate rapidly any electrification of a static character. Another method which promises to be valuable is to use electrically conducting rubber for tyres, tubing, and breathing bags. An account of the work carried out at the laboratory is to be given by Mr. E. H. Rayner, D.Sc., before the Institution of Electrical Engineers, but the director has asked us to call attention now to the methods which can be adopted for minimising the risks. Dr. Rayner has already pointed out elsewhere [2] that static electricity is unlikely to be a danger as long as the atmosphere of the operating theatre has a relative humidity of at least 65 per cent. It seems that in America, where the air in the theatre is likely to become much drier than this when the outside temperature is very low, the danger from static electricity is more of an everyday experience and has stimulated the movement to condition the air in the theatres.

[1] *Lancet*, 1935, **2**, 1327.

PARAGANGLIOMA

IN a case of paraganglioma, Beer, King, and Prinzmetal [3] claim to have demonstrated a pressor substance in the blood during hypertensive crises. Their patient, a woman of 26, was admitted to hospital with a long history of hypertensive attacks. She had previously had a subtotal thyroidectomy without relief, on an erroneous diagnosis of hyperthyroidism. The nature of the attacks was confirmed by repeated blood-pressure readings during her stay in hospital, and the tumour was successfully removed. During an attack in which the systolic blood pressure rose to over 300 mm. Hg, some blood was taken from a vein and the plasma used, with a control plasma, for perfusion of the denervated ear of a rabbit. The perfusion was started with the control plasma and after the pressure as shown by a manometer had become steady the patient's plasma was substituted. This process was repeated three times, and on each occasion the patient's plasma produced a pronounced rise of pressure. This effect could no longer be produced after the ear had been perfused with a 1: 300,000 solution of ergotamine tartrate. These observations suggest the presence of adrenaline or an adrenaline-like body in the circulating blood, and support the clinical theories as to the nature of the tumour. After the tumour (which weighed 290 grammes) had been removed the perfusion experiment was repeated and it was found that the pressor substance could no longer be demonstrated in the plasma. There were no more hypertensive attacks from the day of the operation.

[2] *Lancet*, 1936, **2**, 1408.

[3] Beer, E., King, F. J., and Prinzmetal, M., *Ann. Surg.* July, 1937, p. 85.

SPECIAL ARTICLES

THE GENETICS OF CANCER IN THE MOUSE

By P. A. Gorer, B.Sc. Lond., M.R.C.S. Eng.

(From the Lister Institute, London)

Since cancer is such a mysterious disease and for many years no external cause could be discovered many people thought that this would have to be sought within the organism itself and thus an intrinsic hereditary cause was postulated.

Nowadays only those with an extremely superficial knowledge of genetics regard heredity and environment as two mutually exclusive causes. There are, of course, certain morbid traits, only found in individuals of a certain genetic constitution, which appear to be unmodifiable by changing the environment. Under these conditions it is customary to speak of the disease as due to heredity but it must be remembered that these are really limiting cases. So far as cancer is concerned, we must regard genetic factors as influencing the sensitivity of the organism to carcinogenic agents occurring either in the external environment, or, as in the case of mammary cancer, apparently produced by the organism itself.

It is not necessary to examine in great detail the means by which geneticists reached the conclusion that susceptibility to mammary cancer in the mouse was subject to genetic variation, but it is essential to understand some of the difficulties underlying the genetical analysis and to show how these were partially overcome. The fact that cancer arises late in life is not the major difficulty. If cancer in the mouse always occurred between the 12th and 14th month it would not be very difficult to obtain a fairly accurate estimate of the genetic basis. The great difficulty lies in the fact that there is apparently no upper limit to the cancer age; suppose we have three mice of which one dies of mammary cancer 6 months old, the second dies cancer-free at 15 months, and the third dies of mammary cancer at 2 years, what can we say of the genetic constitution of the cancer-free mouse? This difficulty would appear to be insuperable; we are obviously dealing with a very complex interaction of heredity and environment. At the present stage of our knowledge of the pathology of cancer it is not possible to standardise the environment, but by developments in the theory and practice of inbreeding it is possible to obtain a very fair standardisation of genetic material. Numerous systems of inbreeding have been studied but only brother-sister inbreeding need concern us here. Inbreeding tends to increase the number of genes for which animals are homozygous, and it is possible to show that a very close approximation to a genetically homogeneous population can be obtained after from 20–30 generations of brother-sister inbreeding. Some of the limitations of the theory have recently been considered by Haldane (1936), but provided inbreeding is not relaxed, selection will tend to keep the line homogeneous for all genes affecting the character selected. Strong (1934) has studied the cancer incidence in a line that had been brother-sister inbred for over 20 generations. In the breeding females mammary tumours were found to occur at ages varying from about 4 months to 2 years. Strong deliberately tried to separate sub-lines by selective breeding from animals developing tumours at each of these extremes, but such selection had no effect. Furthermore, Strong (1936) and others have shown that genetically pure stocks do not fall sharply into two groups as far as mammary cancer is concerned, and that it is possible to obtain such strains in which the mammary cancer incidence may take almost any value from 0–85 per cent. This shows quite clearly that mammary cancer is not due to the action of a single gene.

Some years ago Lathrop and Loeb (1918) performed some crosses with strains of mice showing different incidences of mammary tumours. They obtained the somewhat surprising result that the incidence in F_1 hybrids tended to resemble that shown by the strain from which the mother was derived. This result appears to have attracted no attention, and indeed Bernstein (1930) thought that all the results reported by these authors could be explained on the hypothesis of a single recessive gene for mammary cancer. Since work with genetically purified stocks has shown that this view is untenable, there is no need to consider it further here.

HYBRIDISATION BETWEEN PURE LINES

It was not until 1933 that reports appeared of the results of hybridisation between pure lines. The preliminary report (Little 1933) fully confirmed the results obtained by Lathrop and Loeb, and since then similar results have been reported by Korteweg (1936, 1937) in Holland, and by Pybus and Miller (1936) in this country. The more important extensions of this work have been made by Little and his colleagues in America.

W. S. Murray and Little (1935) selected a strain of mice (dilute brown) in which about half the *virgin* females above the age of 8 months died of mammary cancer; this strain appeared to be specially suitable for genetic work since about half the deaths in each age-group above 8 months were due to cancer. The other strain (C.57 Black) had been brother-sister inbred for ten years and no mammary tumours had been observed; a life table showed the ages of death of 240 *breeding* females none of which died of cancer. It was found that both the F_1 and F_2 generations derived from the dilute brown female had an incidence of from 35–40 per cent. When the female parent came from the black strain the incidence in both these generations was about 6 per cent. In a later paper published in 1936, these authors studied the results of various backcrosses only two of which need be described. For convenience the hybrid derived from the dilute brown *female* will be described as the $dB.F_1$ and the reciprocal cross as the $Bd.F_1$. If the inheritance of susceptibility to mammary cancer is mendelian, $dB.F_1$ females backcrossed to black males ought to give offspring with a much lower tumour incidence than $Bd.F_1$ females crossed to dilute brown males. However the reverse was found, and the other backcrosses showed that the incidence of mammary cancer in hybrid generations was not explicable along mendelian lines.

Superficially these results strongly suggest cytoplasmic inheritance, a phenomenon well known in plants, but recent work by Bittner and Little (1937) shows that this is not so. It was shown that if females from a high cancer line were fostered by mothers from a low cancer line, the tumour incidence was much reduced. Little has carried the work further by transferring tubal ova from a high cancer line to the uteri of low cancer females. Sixty-one such mice have lived over six months and a number were

still living at the time of publication (41 mice with an average age of 11·5 months) and no tumours have developed. A few mice from the C.57 Black strain have been fostered by mothers from a high cancer strain and have developed cancer. Bittner and Little therefore advanced the hypothesis that "the extra-chromosomal or maternal influence may tentatively be attributed as due to a breast-cancer-producing influence obtained by the progeny from the milk of high cancer line mothers." This "influence" would probably be described as a virus by many workers, and future work may do much to strengthen this idea, but there are certain facts which are extremely difficult to explain satisfactorily on any hypothesis. For example, Bittner (1936) crossed two high cancer strains, with an incidence in breeding females of 60 and 75 per cent. respectively. When the mother came from the former strain the incidence in F_1 breeders was about 60 per cent., but when the reciprocal cross was performed the incidence was about 80 per cent. Furthermore, there is evidence that genetic factors influence the sensitivity of individuals to the milk-borne agent. Cloudman and Little (1936) showed that if different low cancer males are crossed to the same high cancer female, the incidence in virgin females is different in the two F_1 generations. In one such cross the incidence in the F_1 hybrid was actually higher than in the high cancer pure line (77 per cent. as contrasted with 50 per cent.). For further discussion on this finding the original paper must be consulted. Strong (1936) has also obtained evidence that genetic factors are important by selecting four pure lines with widely different tumour incidences from the progeny of one hybrid female that developed 3 mammary tumours.

The study of leukæmia throws an interesting light on these problems. MacDowell and Richter crossed a pure line with 90 per cent. leukæmia to another line with only a sporadic incidence of the disease. If the female came from the leukæmic line the incidence in F_1 was about 62 per cent., whilst in the reciprocal cross it was about 42 per cent. The existence of extra-chromosomal factors was confirmed by backcrossing. It was shown that no agent was passed during suckling (see MacDowell 1936, MacDowell and Richter 1935, and Richter and MacDowell 1935). In this case there is no information as to the nature of the maternal influence, and the evidence for the importance of chromosomal factors is rather more clear than is the case with mammary cancer. It may be mentioned that cases are known in which extra-chromosomal factors appear to be involved but in which the presence of any agent need not be considered—e.g., in the determination of body size.

Susceptibility to lung tumours seems definitely to depend upon chromosomal factors. Lynch (1926, 1931), whose lines were not as closely inbred as could be desired, gave evidence to show that this was so, and her finding has been confirmed by Bittner and Little. It appears as though one or two partially dominant genes have a very marked effect on the incidence of this type of growth.

Other types of growth have been less thoroughly studied than those listed above. In some cases it may be found that the genetic basis is quite simple, but it is obvious that the theories put forward by Maud Slye (1928, 1931) are no longer tenable.

SUMMARY AND CONCLUSIONS

1. Genetic factors must be regarded as influencing the sensitivity of the organism to environmental factors capable of initiating malignancy.

2. Some of the difficulties involved in an analysis of the genetic factors are pointed out and the necessity for genetically purified stocks is stressed.

3. Pure lines of mice can be obtained in which the incidence of mammary tumours may take almost any value from less than 1 per cent. to over 80 per cent. This fact alone eliminates the hypothesis of a single gene for mammary cancer.

4. The differences observed between pure lines cannot be satisfactorily explained along mendelian lines. The incidence of mammary cancer is in part determined by an agent passed in the mother's milk during suckling. It is probable that chromosomal factors (genes) determine the susceptibility to this agent.

5. Leukæmia shows some of the features exhibited by mammary tumours, but no agent is passed during suckling. There is strong evidence that chromosomal factors play a part in the incidence of the disease.

6. Susceptibility to lung tumours does not appear to be influenced by non-chromosomal factors. It is probable that one or two partially dominant genes play an important part in the incidence of such growths

7. Other types of growth have not yet been adequately analysed. No form of cancer in the mouse has yet been shown to behave as a mendelian recessive.

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A MEDICAL CONGRESS IN THE ROCKY MOUNTAINS

(FROM AN OCCASIONAL CORRESPONDENT)

I HAVE referred previously to the difficulties of holding medical conventions in the wide open spaces of the West: physicians are scattered so thinly over so vast an area that even a State medical society has trouble in collecting an annual audience large enough to make a good conference. In September, 1935, the Colorado State Society adopted a resolution suggesting to its neighbour States of Utah, Wyoming, and New Mexico, that a joint meeting be held in the summer of 1937. The suggestion was approved formally by the medical societies of each of these States, and the first Rocky Mountain Medical Conference has just been held in Denver (July 19th, 20th, and 21st). I was told at the registration desk on the last day of the conference that at that time 786 physicians had registered. A list of names and

addresses showed that quite a number had come from other than the sponsoring States. Kansas was well represented and there were several delegates from Texas and Nebraska. If some members of the conference travelled 1000 miles to the meeting at Denver, some of the speakers travelled double that distance, from New York, Baltimore, and Washington. The highest praise is due to the organising committee for the quality of the lecture programme, the excellence of the scientific exhibits, and the clockwork organisation which started and ended every event exactly on schedule. The new film on syphilis prepared by the American Medical Association and the U.S. Public Health Service was shown for the first time this side of the Mississippi. It is an excellent presentation for medical education, and deserves the widest exhibition in medical circles. The presence of Surgeon-General Parran of the United States Public Health Service at this conference reinforced the teaching of this film. He pointed out that 60,000 babies are still born every year with congenital syphilis, although we know very well how to prevent this disaster. He emphasised also the necessity for using serological tests at every opportunity: on all hospital admissions, at every physical examination, as a routine before-marriage, and so forth. Dr. Parran calculates that 1 in every 5 men and 3 in every 5 women are ignorant of the fact that they have syphilis when they get to the doctor's office. Only 1 in 4 who start treatment receive sufficient to prevent infectious relapse. Prof. C. C. Dennie of the University of Kansas showed some slides illustrating the remarkable success of pyrotherapy as an adjuvant to chemotherapeutic methods in the treatment of syphilis, and especially in the treatment of keratitis and other forms of congenital syphilis. In the absence of the more expensive apparatus such as is used in Dayton, Ohio, Dr. Dennie has been able to reach his desired goal in body temperature by the use of hot baths.

Prof. Walter Alvarez (Mayo Clinic, Rochester), insisting that 4 out of every 5 cases of indigestion are functional in origin, said that the diagnosis of functional disorder should be made from the case-history and not by exclusion. He told a number of dramatic stories to illustrate how often useless surgery is performed for want of thorough history taking. A reaction is very evident in the United States at the present time against over-reliance on laboratory reports and a re-emphasis of the classical methods of diagnosis.

The second Rocky Mountain Medical Conference is to be held in Utah in 1939.

A HUNTER MEMORIAL

A MEMORIAL in honour of William and John Hunter was unveiled at East Kilbride on July 28th by Sir Hector J. W. Hetherington, principal of Glasgow University, who paid high tribute to the brothers' achievements. The enterprise, he said, was begun some years ago, when it was thought that to commemorate these great men a visible memorial should be erected in the parish of their birth. The brothers differed in opinion but their careers ran strangely parallel courses; they were admitted to the Royal Society of London in the same year, both did remarkable work for medical science. Both were founders of a great museum, and both of them were honoured in the institutions with which their names have become associated.

Considered as men of science there was no doubt, however, that John, the younger brother, was the greater of the two. In experiment and observation he was a man of original and outstanding genius. William was also distinguished in science but he was more catholic in learning and taste, more varied in his collecting, and more firmly attached to his place of origin. He was the greatest benefactor the University of Glasgow had known, and his collections were the foundation not only of the Hunterian Museum itself but of many collections associated with different departments of science in the University.

The memorial is to be placed in the charge of the

[*Photograph by Hugh F. Dewar*

Fifth District Council of Lanarkshire. The work is by Mr. Benno Schotz, A.R.S.A., and it is about ten feet high and eight feet broad. It bears a symbolic relief carving, with a bronze panel containing the following inscription, "To the memory of William Hunter, M.D., F.R.S. 1718–1783, and John Hunter, F.R.S. 1726–1793. They were born at Long Calderwood, and died in London after attaining the highest eminence in the sciences of medicine and biology. Their names will be held in reverent remembrance by a grateful posterity to all generations."

WELFARE OF THE BLIND

At irregular intervals the Minister of Health publishes reports made to him by his Advisory Committee on the Welfare of the Blind, first appointed in December, 1917. The twelfth of these reports issued this month (H.M. Stat. Office, 6*d.*) deals with the work of the committee during its life of three years, and is accompanied by a report (Ibid., 3*d.*) to them by a subcommittee on home teaching. The constitution of the committee is such as to give a balanced opinion on the various problems arising, consisting as it does of nominees of local authorities, persons with special experience of the work, and two representatives of organisations of blind persons.

This constitution is of special value in the consideration of such questions as the use of workshops for the blind and the wages of workers, the remuneration of blind workers, and home teaching. To the first of these questions a considerable section of the report is devoted, and the result of negotiations with the National Association of Workshops for the Blind and the National League of the Blind is given in some detail. There is general agreement that the workshops should be places of good workmanship and not be mere occupation centres, and that wages should be based on piecework, with generous augmentation, while there should be proper safeguards for low wage earners. Somewhat similar questions arise in connexion with home workers, and the committee regret that some local authorities have not seen fit to deal with their augmentation in a more generous spirit.

INCIDENCE AND PREVENTION

Till recently information of the incidence of blindness was incomplete, and at least a part of the increase in the numbers given in the Table on p. 12 of the report is due to improved registration. The increase there shown is from 25,840 in 1919 to 67,534 (1 in 603 of the population) in 1936. The analysis of the age distribution in 1932 and 1936 shows a considerable fall in the numbers at ages below 40 years and a large part of the rise in the 40–50 years group is attributed to the passing of war blinded persons to the next higher group, viz., increase only at 70 years and over. Even more satisfactory information is given in a more detailed Table from 1919 onwards, showing large falls at all ages below 50 years. The decrease of blindness in children may be due, it is remarked, to a variety of causes, but undoubtedly the ophthalmia neonatorum regulations have been instrumental to a large extent in reducing the number of cases of blindness due to this disease. The committee observe that information is not yet available on which a detailed classification and analysis can be made of the causes of blindness, and attention is directed to the investigation being made by a standing committee of the Union of Counties Association which is examining the certificates of notification framed on the detailed form issued by them.

The Minister of Health has also issued a memorandum (Circular 1621, dated August 6th, 1937) dealing with the prevention of blindness under various headings. He refers to the wide powers possessed by local authorities for the treatment of persons, including those with any disease of and injury to the eyes, and observes that from Oct. 1st next when the Public Health Act, 1936, comes into operation formal consent of the Minister to arrangements for treatment will no longer be required. The proposals in the circular are based on the report of the standing committee already mentioned, and deal with antenatal services, ophthalmia neonatorum, children under and over school age, infectious diseases, venereal diseases and accidents. In the circular is included a model scheme, the basis of which is voluntary notification of the occurrence of cases at a fee of 2*s.* 6*d.* or such other sum as the local authority may determine, and subsequent care and treatment on behalf of the authority. Two points of detail mentioned are prophylactic drops in the eyes of infants and appropriate forms of instruction for myopic children. As regards the former the committee are not prepared to insist on the need for prophylactic drugs as a routine measure and consider that the proper cleansing of the baby's eyes at birth is the first essential. On the second point, the committee would like to see further inquiry into the influence of myopia in causing blindness and the part played by the special school for partially sighted children in preventing such blindness.

PENSIONS AND EMPLOYMENT

The annual expenditure of local authorities under the Blind Persons Act, 1920, which has been slightly over £1,000,000 in each of the last three years, works out at £16 per blind person. This amount does not include the old-age pensions payable to blind persons over 50. Satisfaction is expressed at the Minister's announcement of September, 1936, to give effect to the proposed reduction of the age from 50 years to 40 years, and it is hoped that the arrangement whereby pensions officers keep in touch with local authorities will obviate difficulties which have arisen in the past from conflict between decisions as to blindness for old age pensions and for registration purposes. The central consultative committee are continuing their activities on behalf of the deaf-blind and, with a view to obtaining guidance in ways of making suitable provision for them, have placed an organiser in the northern counties area to survey the position, his salary being paid out of a grant from the National Institute for the Blind.

Progress is being made with the provision of talking books; 600 machines of the gramophone type with discs running at 24 revolutions per minute are already in use and 50 books have been produced by the sound recording committee of the National Institute for the Blind, of which Sir Ian Fraser is chairman. Generous contributions have been received from various sources, including £35,000 (14 half-yearly gifts of £2500) from Lord Nuffield. Further experiments are being conducted out of these funds with a view to finding the most suitable form of reproduction; a film form has definite advantages in portability and wear. Meanwhile gramophone talking books can be purchased for £5 10*s.* (electrically driven) or £3 10*s.* (mechanical machines). The books are lent from the talking book library, which has 40 records from the United States, in addition to the 50 mentioned above. By arrangement with the Post Office a talking book weighing 11 lb. can be sent by post for twopence.

MEDICINE AND THE LAW

Manslaughter by Dangerous Driving

SUICIDES who take their lives by jumping from a height probably do not take account of the injuries they may inflict on innocent passers-by. At a Paddington inquest a fortnight ago it was found that a woman who jumped to her death from the upper floor of buildings at the back of New Oxford-street had struck a young man of 18 who was walking along the pavement. He died in hospital a few hours later. Mr. Ingleby Oddie sensibly refrained from recording a verdict of murder, though in the text-books there is much which would justify such a course. In R. *v.* Hopwood (1913) it was established that, if a man fires at himself with intent to commit suicide and kills somebody else, it is murder.

Killing without intention, while doing some other act, may be either homicide by misadventure, manslaughter, or murder, according to the nature of the act. A man is working with a hatchet; the head flies off by accident and kills a bystander; this is homicide by misadventure. A man shoots at his neighbour's poultry, intending to steal them, and kills a neighbour; this is murder because the killing occurs in the course of committing a felony. If he shoots at the poultry without that intent and kills his neighbour, it is merely manslaughter because his act was unlawful but not felonious. The law of constructive murder had its classic exposition in R. *v.* Beard (1920), a case referred to last month in the Court of Criminal Appeal when counsel for an appellant tried in vain to argue that the law was becoming more lenient. The jury found that Beard, while committing the felony of rape, choked his victim to death by putting his fingers on her throat to keep her quiet. Perhaps the most frequent occasion for considering constructive murder or manslaughter arises where death follows a criminal abortion. Judges usually tell the jury that, if they think the deceased woman died as a result of the prisoner's unlawful operation, it is murder; if they think the prisoner could not reasonably have expected death to result, they may find a verdict of manslaughter.

Mr. Ingleby Oddie was the more inclined to rule out the verdict of constructive murder because the similar principle of constructive manslaughter is so little applied in cases of dangerous driving. Almost every day, he said, somebody is killed by a motorist who is driving dangerously. Anybody driving to the public danger is committing an unlawful act; if he causes death by dangerous driving, it might be supposed that he would be found guilty of manslaughter. Yet it frequently happens that no charge of manslaughter is made in these cases of homicide; the driver is charged with dangerous driving and is punished for that offence although in strict law it is manslaughter.

The relation of manslaughter and dangerous driving is discussed in the current *Law Quarterly Review* in an able article by Mr. Patrick Dean. Mr. Dean points out the difficulties which arise because of the many grades of negligence punishable under the Road Traffic Act. He shows that lately, in Andrews *v.* Director of Public Prosecutions, the House of Lords had a rare chance to clear away doubts, yet failed to use it. Under Section 11 of the Road Traffic Act of 1930 it is an offence to drive a motor vehicle on a road recklessly or at a speed or in a manner which is dangerous to the public, having regard to all the circumstances of the case, including the nature, condition and use of the road and the amount of traffic which is actually at the time (or might reasonably be expected to be) on the road. This rather cumbrous section is plainly more serious than driving "without due care or attention or without reasonable consideration for other people using the road," which is an offence under Section 12 of the Act. In the Andrews case the following question arose. Suppose that a motorist is driving in such a manner that, if no death occurred, he would have been convicted under Section 11. Now suppose that death does occur; is the fact that the motorist's manner of driving was unlawful (as contravening Section 11) enough to require a conviction of manslaughter? Lord Atkin said that on the trial of a motorist for manslaughter (when, under Section 34 of the Road Traffic Act, 1934, the jury may convict of the lesser offence of dangerous driving) the judge ought first to direct the jury as to the high degree of negligence necessary for manslaughter; he ought next to explain that this is not necessarily the same degree of negligence as is required for the offence of dangerous driving; thirdly he ought to indicate the conditions under which the jury may acquit the driver of the more serious, and convict him of the less serious, offence. As Mr. Dean observes, this omits to tell us what those conditions are. We are no wiser as to the difference between the degree of negligence which is an ingredient in dangerous driving and the degree of negligence which amounts to manslaughter. Lord Atkin referred to R. *v.* Bateman (1925), which was a question of professional negligence. Lord Hewart's judgment in the Bateman case threw much light upon the difference between the standards of civil and criminal negligence, but was not concerned to analyse the negligence of motorists. Mr. Dean would have liked more light upon the mental element in manslaughter and its relation to the mental element in other offences. He suggests that this question is suitable for consideration by the Lord Chancellor's Law Revision Committee. It would certainly seem that the judges owe us a clarification of the law; they have befogged us with a wide range of epithets applied to negligence—"wicked," "culpable," "criminal," "gross," "clear," and "complete."

IRELAND

(FROM OUR OWN CORRESPONDENT)

THE MILK QUESTION

IN his annual report on the health of his county Dr. J. A. Musgrave, county medical officer of health for Louth, devotes some space to the consideration of milk from the point of view of health. He states that poor people do not drink it to any extent, not because it is expensive, but because, being a drink, it is not regarded as a food, while money is spent on heavier foods of much less nutritional value. He cannot at present join in the "Drink More Milk" campaign, because the purity of the milk-supply is not yet guaranteed. Bovine tuberculosis is still a menace in Ireland, whereas in countries where severe legislation in regard to milk is enforced it is said to have almost disappeared. Efficient veterinary inspection is essential to eliminate the dangers of tuberculosis, and the strictest regard to an adequate code is necessary to ensure cleanliness. Both are provided for in the Milk and Dairies Act. If a scheme of regular sampling of milk-supplies entering urban areas were adopted it would have a good effect. Notwithstanding

the improvement in the cleanliness of dairies in recent years the death-rate from non-pulmonary tuberculosis remained constant, while the pulmonary rate had fallen. In Dr. Musgrave's opinion pasteurisation was at present the only way to guarantee an absolutely safe milk-supply. He urged that the provisions of the Milk and Dairies Act should be rigorously applied. "If we take an easy line and operate the new Act without reasonable stringency, there will be just as much irritation, opposition, and friction, and no other result save a waste of public money."

Synchronously with the publication of Dr. Musgrave's report, the Society of Medical Officers of Health of the Irish Free State has been drawing timely attention to the danger to health arising from the present methods of working the creameries. This danger was the subject of comment in the Dáil while the Milk and Dairies Bill was under discussion but was pooh-poohed by the Minister. The resolution of the Society of Medical Officers of Health draws the attention of the departments concerned to the danger arising from the present method of dealing with skim milk by the creameries throughout the country. The milk from the suppliers to a creamery is mixed in the creamery and, after the cream has been separated, the skim is returned to the various suppliers without pasteurisation.

"It is certain," so runs the resolution, "that some tuberculous milk reaches each creamery, and, thus, it is probable that a large number of suppliers will receive back skim milk infected with tubercle bacilli. The high incidence of tuberculosis in pigs slaughtered for bacon at the age of about seven months proves that the pigs were exposed to gross infection from tubercle bacilli, and it seems certain that the vehicle of infection was the skim on which they were fed. We would point out to the Department of Local Government and Public Health the gravity of this matter and ask that steps be taken to enforce the pasteurisation of skim milk in the creameries."

IRISH FREE STATE MEDICAL REGISTRATION COUNCIL

Dr. Robert J. Rowlette and Mr. William Doolin, the only candidates nominated, have been re-elected as direct representatives of the registered practitioners on the Irish Free State Medical Registration Council for the period of five years from Oct. 24th, 1937.

GRAINS AND SCRUPLES

Under this heading appear week by week the unfettered thoughts of doctors in various occupations. Each contributor is responsible for the section for a month; his name can be seen later in the half-yearly index.

FROM F.R.C.S. (1936)

III

To write of engagements one week and divorce the next suggests that frivolous attitude towards marriage which was strongly deplored by both proposers and opposers in the recent debates on the Matrimonial Causes Bill. An introductory denial of any such feeling is therefore apposite. During its early days in the House of Lords the Bill looked as though it might produce a professional line-up and result in a three-cornered tilt between the learned professions there represented. From this point of view unhappily there was a lack of team spirit amongst the lawyers and the clergy, and official medicine alone presented an unbroken front. A legal or clerical partisan might well say that in a debating team of one it would be hard to contrive it otherwise, and the answer would be that the leader of the Lords Spiritual showed that it was easily within his powers to afford lukewarm support for Clause 1 in its original 5 year form, oppose its reduction to 3 years, vote for its complete abolition, and to announce a general policy of abstention on the Bill. In the face of such versatility it is a matter of greater regret that medical representation in the House of Lords is limited to that very eminent and busy minority whose attendances can only take place at the sacrifice of professional work which in any case precludes continuous political activity.

Mr. Herbert's Bill provides an excellent example of that type of legislation on which medical opinion is at least as necessary and pertinent as that of the Lords Spiritual. The admission of, say, the honorary physicians to His Majesty as temporary Lords Medical would add lasting catholicity to that heterogeneous seven hundred and in no way lower the standard of oratory.

* * *

A closer study of the Matrimonial Causes Bill itself will no doubt clear up many points of uncertainty left by the reports in the lay press, as it is difficult to believe that Mr. Herbert would leave obscure the definition of the specifically mentioned medical conditions. Nevertheless those clauses dealing with medical conditions justified a more technical debate than they obtained. It was inevitable that such attention would be largely focused on the clause permitting insanity of five years' standing as a ground for divorce, and this opportunity was not missed by those peers who held views of their own on the ætiology and treatment of the psychoses. On this question adequate reports were obtainable and it is rather regarding the annulment clauses for which one awaits the opportunity to read the Bill for further enlightenment. How for example is epilepsy defined? It is difficult to conceive a definition of "idiopathic" epilepsy which would be practicable for this purpose, and from reports it is not possible to learn if it is the intention of the Bill to exclude symptomatic epilepsy. The presumption is that it is meant to be excluded, or the anomalous position could arise of, for example, one case of cerebral tumour being liable to annulment of marriage on account of fits while a second whose neoplasm presented as a hemiplegia would be subject to no such penalty.

* * *

It is even less easy to gauge the exact position regarding the clause which includes venereal disease, present before marriage and unknown to the innocent party, as a cause for annulment. Here there is plenty of room for speculation. Is a soft chancre or scabies contracted during sexual intercourse as good grounds for annulment as a condyloma or a urethritis? Nor is it easy to understand the inclusion of this clause in a 1937 Bill; it would seem to denote an attitude towards venereal disease which is more superstitious than medical. Even supposing the marriage has taken place during an infective period there can be little social benefit in separating two infected individuals; compulsory treatment would deal with the situation better. Technical points, one can feel

certain, are more than adequately defined in this Bill, but it is to be regretted that informed debate on the medical aspects seems to have been left to one Member of the House. In such matters adequate representation of the medical profession is perhaps more necessary in the House of Lords than the Commons. The Lords have shown that on such social issues as arouse the opposition of organised minorities their imperviousness to the votes of the electorate makes them the more progressive of the two houses, and the future may constantly present us with the picture, that Lord Ponsonby found so diverting, of the Lords liberalising a die-hard Commons measure. By so doing they rectify a defect in the democratic system which allows a fear of alienating the voter to impede the progress of necessary legislation. It is thus rather to the Lords to whom we must look in hope, however faint, for the Bill which will abolish the cyclist from the high roads and confine him to special tracks. There are no obvious grounds for urging full medical representation during the presentation of such a Bill, but it is a melancholy thought that the initiation of such spacious legislation rests so largely on the law and even on the "brutal and licentious soldiery" rather than on the medical profession.

* * *

At the conclusion of the Wembley exhibition British supremacy in the European field had been clearly established in respect of amusement parks. A visit to Paris in 1937 makes it clear that that dominant position remains unchallenged. The Paris exhibition provides the spectator with a design almost perfect for the best display of the beauties of that city, of its Seine, and of its Eiffel Tower. It is the Tower which captures the attention and dominates this exhibition as it did that of its origin. From the Trocadero across the fountains, the Seine, and the flanking pavilions it stands an unforgettable picture of architectural grace and beauty. It is the attribute which gives coherence and character to the whole lovely design, and the odd thing is that the French apparently find it as satisfying as the stranger and give it and the pavilions an avid attention which is at home reserved for the amusement park. The pavilions themselves are as varied in quality as in nature and it is the smaller countries—Belgium, Denmark, Holland—who have best mastered the art of displaying their industrial resources and natural beauties, without obstrusive propaganda. Of the totalitarian States the massive German pavilion makes a good flank to the vista from the Trocadero. On its tower a slightly self-conscious eagle half turns its head from the agitated challenge flung across the avenue by the two proletarian figures occupying a similar position on the U.S.S.R. pavilion, which has been nicely placed immediately opposite. Germany's neighbour on the right is Spain, with its chief exhibit Picasso's nightmare conception of Guernica. A happy spirit of camaradie can be expected to envelop this corner of the exhibition after hours.

* * *

The British pavilion clearly illustrates that the amusement park might have been twice as elaborated without injury to our island reputation as the country where *le sport* is best appreciated. This pavilion has been the target of a quantity of misconceived criticism. There are those who would have had it a composite British Industries Fair, and others would have looked forward to seeing it constitute a testament to democracy challenging the rival political creeds of neighbouring pavilions. The organisers can be congratulated on their grasp of the political situation and the manner in which they have solved the problem before them. Of recent years there has been a growth abroad of the impression that the Englishman was starting to take things seriously, was indeed ceasing to be an amateur. If this calumny has not quite been killed at birth it can at least be expected to perish instantly in the minds of all Frenchmen who visit the exhibition. Numbed by seried models of German machinery, endless photographs of Stalin, repeated statistics of Russia's cultural development, and examples of Italian heavy industries, the weary brain is jolted to activity immediately on entry into the British main hall. Here all round the walls are tennis rackets, rods, cricket bats, saddles, golf clubs, crops, hockey sticks, and croquet mallets; Gamage's window has been reproduced with startling similitude. With mental refreshment comes the reassurance that our amateur status is secure and likely to remain so. Although there are some agricultural implements in the basement one feels that they are only for use by gentleman farmers.

PUBLIC HEALTH

Steps Towards National Fitness

By introducing their Physical Training and Recreation Act and by appointing a national council and a grants committee to assist in carrying it out, the present Government has given further practical proof of its determination to do all it can to promote physical fitness in persons of all ages throughout the country. Certain measures are to be embarked upon immediately, and these are summarised in a booklet entitled "National Fitness: The First Steps" (H.M. Stat. Office. Pp. 24. 2*d*.). Twenty-two area committees, who should be in action by Oct. 1st, will supervise the working of the Act in all parts of England and Wales. Through them grants ranging, according to local economic conditions, from 25–75 per cent. of the total capital outlay involved, will be made to finance the provision of playing-fields, running and cycling tracks, hostels for hikers and cyclists, camping grounds and swimming baths, community centres for indoor games, gymnastics, and physical training. Except in cases of special hardship, the costs of maintenance will devolve upon voluntary organisations or upon education or other local authorities, but the latter are given powers by the Act which will enable them to meet these costs. A national college is to be instituted where courses of varying length will be held for part- or full-time teachers of physical training, and, as an experiment, education authorities and voluntary organisations will be given financial help for a limited period towards the salaries of such teachers where full employment can be found for them. The success or otherwise of these measures must ultimately depend upon the amount of support accorded to them by public opinion, and suitable propaganda will help to develop it. If sufficient support is forthcoming—and there seems no reason to suppose that it will not—the expenditure of money and effort should show a return in national efficiency and personal happiness.

The L.C.C. Ambulance Service for Accidents

The account of the ambulance service provided by the L.C.C. for accidents in streets and public places

for the year 1936 supplies a record of progressive and efficient administration. It will be recalled that the passage of the Metropolitan Ambulances Act of 1909 received little encouragement, in its earlier stages, from the House of Lords, the Home Office, or the police, and indeed for some years after it was placed on the Statute book the Council refrained from putting the Act into operation. There are now 16 ambulance stations served by 25 motor ambulances, and in an average time of less than 7 minutes from the receipt of a call an ambulance is at the site of the accident. Over 53,000 calls were received during 1936 as against 40,638 in 1932. Calls were most frequent between the hours of noon and 2 P.M. and between 6 and 8 P.M., and more calls were received on Saturdays than on any other day of the week. The Bloomsbury station was that most frequently called into requisition, but Lambeth and Westminster appear to have been the areas in which the greatest number of accidents occurred. The service is available not only for cases of sudden illness but also for cases of parturition, and calls for these emergencies represent a considerable number of the total requisitions. Over 18,000 summonses for the ambulances were received from the Metropolitan Police, and nearly 26,000 from members of the public who are evidently becoming aware of the excellent service at their disposal. The destinations to which the victims of accident are conveyed is of interest. Last year 19,342 were taken to London voluntary hospitals and 26,291 to L.C.C. hospitals or municipal institutions; of the latter St. James' Hospital, Balham, and the Lewisham Hospital claimed the largest number of admissions. Only those who recall the methods employed in conveying injured and sick persons to hospitals before the institution of this beneficent municipal service can realise the amount of risk, suffering, and dangerous delay that is now saved.

The Supply of Measles Serum

The efficacy of a timely injection of serum from a measles convalescent or from an adult who has had measles in preventing or attenuating an attack has been proved, and it is clear that its efficient use may reduce the mortality during an epidemic and the debility following severe attacks, besides removing much of the anxiety and inconvenience to which an outbreak gives rise in a school, a children's hospital, or other institution. The supply of convalescent serum is limited and likely to remain so, as it is inadvisable to bleed very young children; many parents are unwilling to have blood taken from their children for the treatment of strangers. Fortunately the serum of young adults who have had measles within ten years has proved nearly as effective and, unless placental extract ultimately supplants it, such adult serum will remain our main source of antibodies. It is obviously desirable that this serum should be readily available throughout the country for use as soon as an epidemic occurs. There is no need for the blood of the donor and the recipient to be of the same group, so that the blood of a child's parents or of one of the young masters in a school can be used in an emergency. In some areas the local authorities have made arrangements for the collection and pooling of serum from volunteers, but this is by no means universal. What is required is some organisation on the lines of the Red Cross transfusion service to supervise collection and distribution, and Dr. Elwin Nash, who is medical officer of health for Heston and Isleworth, has suggested that such supervision might well be entrusted to the Boy Scouts Association, the serum being supplied, as it is in his area, by volunteers from among the rover scouts. In Dr. Nash's opinion it is only in such a movement as this, which carries with it an urge to do things for reasons other than material gain, that there is likely to be an adequate response. This association, however, feels that a general scheme should be devised and adopted by the medical profession before deciding to take part in it. We commend Dr. Nash's suggestion to other members of the public health service.

Valuable Labels

Circular 1639 of the Ministry of Health contains facsimiles of the labels issued by foreign governments which carry the state guarantee of inspection and will be accepted in this country as evidence that foodstuffs imported bearing these labels have been inspected at the place of production in a manner which satisfies our rigid requirements, provided the labels are securely attached and have not been altered. These labels, which are for meat and meat products, are issued by countries which guarantee that their issue is proof that the animals from which the meat was derived were inspected and approved both before and after death, and that all necessary precautions were taken for the prevention of danger to public health in dressing, preparing, and packing. The recognition of these stamps by the Ministry of Health is an important step forward in our campaign to ensure a safe food-supply which should be known to the public, for it will help to remove certain doubts about foreign meat which are still current, although for some time they have had little foundation. The importance of these guarantees is that though disease in carcasses can be detected at any time, pieces of meat, or meat products, may show no detectable signs of disease even if they come from dangerous sources.

INFECTIOUS DISEASE

IN ENGLAND AND WALES DURING THE WEEK ENDED AUGUST 7TH, 1937

Notifications.—The following cases of infectious disease were notified during the week: Small-pox, 0; scarlet fever, 1364; diphtheria, 794; enteric fever, 47; pneumonia (primary or influenzal), 373; puerperal fever, 30; puerperal pyrexia, 138; cerebro-spinal fever, 19; acute poliomyelitis, 20; polio-encephalitis, 4; encephalitis lethargica, 2; dysentery, 10; ophthalmia neonatorum, 129. No case of cholera, plague or typhus fever was notified during the week.

The number of cases in the Infectious Hospitals of the London County Council on August 13th was 2744, which included: Scarlet fever, 677; diphtheria, 666 (diphtheria carriers, 23); measles, 176; whooping-cough, 470; puerperal fever, 18 mothers (plus 11 babies); encephalitis lethargica, 284; poliomyelitis, 4. At St. Margaret's Hospital there were 23 babies (plus 11 mothers) with ophthalmia neonatorum.

Deaths.—In 124 great towns, including London, there was no death from small-pox, 2 (0) from enteric fever, 5 (0) from measles, 3 (1) from scarlet fever, 16 (7) from whooping-cough, 20 (1) from diphtheria, 38 (10) from diarrhœa and enteritis under two years, and 9 (2) from influenza. The figures in parentheses are those for London itself.

Ilford and Southend-on-Sea reported deaths from enteric fever. Diphtheria was fatal in 15 great towns; in 3 cases at Birmingham, in 2 at Salford and Stanley. Liverpool had 6 deaths from diarrhœa, Birmingham 4.

The number of stillbirths notified during the week was 236 (corresponding to a rate of 38 per 1000 total births), including 36 in London.

SURREY COUNTY HOSPITAL, KINGSTON.—It is proposed to convert one of the ward balconies at this hospital into a ward for the accommodation of ten more patients by covering in the balcony with light timber framing with insulated plaster board inside.

CORRESPONDENCE

THE BIRTH STIMULUS AND THE SPAWNING STIMULUS

To the Editor of THE LANCET

SIR,—The absence of knowledge regarding the stimulus for parturition in man and other mammals is paralleled by a similar lack of information as to the spawning stimulus in marine invertebrates. The two groups of cases are essentially similar mechanically in that evacuation of either the fœtus or the genital products is made from a tube closed by a sphincter; hence it is possible that the operating mechanisms may have other common features, and suggestions which apply to one group may at least focus attention to unexpected aspects in the other. In this way progress may be made.

In recent years many surprising observations have been made on rhythmic breeding in marine animals and upon definite periodicity in spawning—i.e., extrusion of genital products, in relation to tidal and therefore the moon's phases.[1] Although in some species it is known that flooding with gametes of one sex may induce spawning in the other, and that spawning is associated with minimum temperature levels, little is known regarding the basic spawning stimulus which is undoubtedly operating. For example, about 45 per cent. of the mature and maturing female population of oysters (*Ostrea edulis*) spawned simultaneously about June 13th–14th, 1936, on the Roach River oyster beds. As even higher proportions may spawn practically simultaneously in other marine species there can be no doubt whatever about the evocation of a common spawning stimulus. Among marine animals external as well as internal factors play a part, and all those factors which change with the tide—namely, temperature, pressure, salinity, alkalinity, light intensity, available food, emanations from opposite sex, and oxygen pressure—may *contribute* towards a spawning stimulus in those individuals which are ready internally to receive it.

I have recently suggested [2] that the most important factor may be the oxygen susceptibility of the gravid individual, for in the course of the development of eggs or sperm oxygen consumption will be high during preparatory and maturing stages, probably attaining a peak at maturity. In the same way oxygen requirements of the fœtus in mammals will increase to a maximum about the time of parturition. It seems likely therefore that in mammals and invertebrates the organism will be hypersensitive to oxygen variation in the late gravid condition. If this susceptibility exists, as seems highly probable, then here is a trigger state in which oxygen variation may in different ways act upon the appropriate nervous centres to set in train the evacuating mechanism. The effect of the stimulus is to cause relaxation of the orifice and contraction or constriction of the tube or tubes. These events must occur in their proper phase to be successful, and it would appear that the administration of any drug or preparation which elicits only the contraction phase, for example of the uterus, may be useless and in some cases definitely harmful.

Some phenomena of parturition in mammals as also of spawning in invertebrates appear to be based on oxygen susceptibility, but extended investigations are needed to reveal the actual course of events; the practical importance of accurate knowledge on the subject is sufficient excuse for drawing attention to the possible analogies given above.

I am, Sir, yours faithfully,

J. H. ORTON.

The University, Liverpool, August 13th.

[1] Fox, H. M. (1924) *Proc. R. Soc.* B, **95**, 523.
[2] Pelseneer Jubilee Volume, *Mém. Mus. Hist. nat. Belg.* 1936.

"NO PLACE FOR AN EPILEPTIC BOY"

To the Editor of THE LANCET

SIR,—With regard to the article under this title on p. 285 of your issue of July 31st, it seems to us that the case described is a mental defective and would be certifiable under the Mental Deficiency Acts, 1913–27, as a moral defective. He would therefore be eligible for admission to any appropriate institution and possibly would be a suitable case for Rampton State Institution.

We are, Sir, yours faithfully,

J. LLOYD,
J. N. JACOBSON.

Fountain Hospital, Tooting Grove, S.W., August 11th.

PASTORAL PSYCHOTHERAPY

To the Editor of THE LANCET

SIR,—This correspondence has certainly called forth some interesting and surprising expressions of opinion and has provided a concrete illustration of the difficulties clinical psychology has to contend with as an important branch of medicine. When mental phenomena are the subject of discussion, it is obvious that the task of maintaining the purely rational attitude becomes a very difficult one.

Dr. Batten quietly begs the whole question in asking if only qualified medical men are fit to minister to sick souls. Sick bodies we know and sick minds we know, but are we to understand that the sick soul is something different from the latter? If so, and if, as Mr. Fletcher claims, pastoral psychotherapy is designed to deal with spiritual disorders of the personality, to avoid confusion and aid differential diagnosis it would be a great help if we could have a brief description of two or three of these spiritual diseases and some indication as to how to separate them from the ordinary psychological disorders. It would, furthermore, be less equivocal if the word "psychotherapy" were given up in this connexion and a distinguishing name like "pastoral spiritotherapy" used in its place—if the purists would not be too horrified at the hybrid.

Dr. Hubble in his admiration for unqualified medical practice makes one wonder if he carries the same admiration into other spheres of life. Does he, for instance, prefer to have his prescriptions dispensed by an unqualified chemist, and does he go to an unqualified solicitor to help him in a legal difficulty? His letter is not without unconscious humour when he describes the patient who underwent "complete cure" of an anxiety state by a minister of religion as having come easily through her relapse. May we be permitted to hope that she will come equally easily through future relapses? Incidentally, is an anxiety state a spiritual disorder of the personality?

Cannot an answer to the questions at issue be put quite briefly in saying that as progress in all other departments of medicine has, with one or two exceptions which do not affect the general principle, been brought about by strict adherence to the scientific

method the high probability is that authentic progress in psychotherapy will be brought about by the same means? I am, Sir, yours faithfully,

FREDERICK DILLON.

Wimpole-street, W., August 15th.

To the Editor of THE LANCET

SIR,—Dr. Clifford Allen is fortunate in that he finds the ideas of those who oppose him "childish." He is less fortunate in that his own views have not as yet commanded the representative support of his brother psychotherapists. There is but one course for him. The Guild, undeterred by his opposition, will continue to sow what he so confidently believes to be tares. He will continue to sow what he believes, with equal confidence, to be wheat of the best quality. And the harvest? Those of us who live till 1960 may see Dr. Allen attending a demonstration of psychotherapeutic technique by the Reverend So-and-So, the distinguished psychotherapist, just as the British Orthopædic Association found itself sitting at the feet of Sir Herbert Barker. Unfortunately we shall be denied any amusement on that occasion for this sprightly controversy will have long since been forgotten.

I am, Sir, yours faithfully,

Derby, August 15th. DOUGLAS HUBBLE.

To the Editor of THE LANCET

SIR,—A cursory comparison of Dr. Clifford Allen's latest letter with his earlier ones to you will make it apparent that he has effectively denied his own argument. Taking to task some of his professional colleagues who have ventured to disagree with him, he accuses them of precisely those mental limitations which, in his view, make the clergy unfit to practise psychotherapy. Having urged that the physician is by training "detached, unemotional, and scientific," Dr. Allen now discovers in his fellow practitioners "ignorant prejudice" and "a great capacity for drawing conclusions with insufficient evidence to support them"; thus contradicting his earlier premises.

Dr. Allen affirms that psychotherapy is a branch of medicine. He seems not to have observed that it is also a branch of psychology. "The basic principles which support the whole" are by no means exclusively the principles of physical medicine. Indeed, one could with some cogency argue that they are essentially philosophical and religious. Certainly, by his own argument, Dr. Allen would have no reason to complain if the philosopher or theologian—and imperatively the metaphysician—should require him to produce evidence of his competence in these sciences, as he would require evidence of medical competence in them, before they acknowledged his qualification to undertake the treatment of personality disorders.

No good service is done to any point of view by an evasion of the difficulties raised both for religion and medicine by psychotherapeutics. Dr. Allen affirms his admiration for the church and his respect for the ministries of religion. If he is sincere in his desire for a scientifically objective attitude to this matter let him consider the real problem raised for all concerned by the psychophysical nature of human personality. Can he provide a definition of psychotherapy that will enable both clergy and doctors to discern where the limitations of both their provinces are in the mutual task of making personalities "whole," bearing in mind the obvious fact that a medical man is no more equipped by his scientific training for the cure of souls than the clergyman is by his training for the cure of bodies? As I have already tried to show, this is a real and pressing problem that deserves consideration with all the scientific detachment and goodwill at the command of everybody concerned, and I am sure that many beside those who are interested in the Guild of Pastoral Psychotherapy will acknowledge their indebtedness to Dr. Allen if he will make a constructive contribution to its solution.

In my previous letter I omitted to say that I shall be glad to post copies of the memorandum about this Guild (a perusal of which led Dr. Allen to write to you) to any of your readers who will send me a card making the request.

I am, Sir, yours faithfully,

A. B. W. FLETCHER,
Hon. Sec., The Guild of Pastoral Psychotherapy.

29, Dorset-square, London, N.W.1, August 16th.

"BIOCHEMICAL CONTROL OF CANCER"

To the Editor of THE LANCET

SIR,—The recent award of a Civil List pension to Dr. Copisarow must be taken to mean that, in some direction, he has done important service to science, with even less reward through normal channels than comes to most research workers. His attempt to solve the cancer problem by biochemical speculation must, accordingly, command a certain respect. The indication, however, of the nature of his theories, in his letter published in your issue of August 7th, by reference to "oxidation enzymes, the glutathione equilibrium, vitamins E, B_1, B_2, &c.," does not convey any clear idea; nor is understanding assisted by the claim that "these conclusions" have now been supported by "experimental evidence from various sources," since much of what is cited has no obvious relevance. Possibly a study of Dr. Copisarow's earlier publications might reveal a greater coherence.

Of much greater importance, however, than Dr. Copisarow's theoretical speculations, is his statement that he has been led by them to a corrective treatment for cancer, and the suggestion that this also has been supported by the assortment of evidence quoted. The treatment consists of two items: (1) the administration of yeast with what is termed an "enzyme-bearing medium, such as unrefined sugar or honey"; and (2) "the injection of certain non-toxic sulphur-labile compounds," of which mustard-gas (dichlorodiethyl sulphide) is, curiously, quoted as an example. One has heard of the simultaneous ingestion of yeast and sugar, as a device for procuring cheaply a thorough alcoholic intoxication, and of the drawback due to the concomitant distension of the stomach with carbon dioxide; but mustard-gas, as a "non-toxic" sulphur derivative suitable for injection, is surely a therapeutic novelty. It is to be hoped that none of your readers will be so much impressed by the show of theory, and the list of references to experimental evidence cited in its support, as to give the suggested treatment a practical trial, without some much clearer and more detailed indication of the way in which its rather obvious disadvantages can be avoided.

I am, Sir, yours faithfully,

August 14th. BIOCHEMIST.

To the Editor of THE LANCET

SIR,—In your issue of August 7th Mr. Copisarow refers to the "recent experimental work of several investigators with methylene-blue" and gives references to two works published in 1933. As I happened to be particularly interested in this subject at the time these articles appeared, I ransacked the London medical libraries for further information

and collected some interesting references of which the following are a selection in chronological order:

Einhorn, M. (1891) *Dtsch. med. Wschr.* **17**, 620.
— (1891) *N.Y. med. Rec.*, **39**, 358.
Mosetig-Moorhof, R. (1892) *Lancet*, **1**, 414.
— (1892) *Wien. klin. Wschr.* **18**, 1.
— (1896) *Zbl. ges. Therap. Wien.* **14**, 1.
Nanu, G. (1892) *Münch. med. Wschr.* **42**, 1018.
d'Ambrosio, A. (1893) *Münch. med. Wschr.* **40**, 634.
Medical Annual, 1893 (review), p. 113.
Mazet, C. (1897) *Marseille méd.* **34**, 394.
Slack, H. R. (1897) *J. Amer. med. Ass.* **28**, 1227.
Jacobi, A. (1906) *N.Y. St. J. Med.* **6**, 367.
— (1906) *J. Amer. med. Ass.* **47**, 1545.

These forgotten works indicate that methylene-blue and methyl-violet (pyoktanin) were used in the treatment of cancer prior to radium, and no doubt they were "put on the shelf" when the latter was introduced. A study of these articles, however, should be of considerable interest to those engaged in scientific work on this subject.

I am, Sir, yours faithfully,
R. PAKENHAM-WALSH.

County Mental Hospital, Lancaster, August 6th.

UNDESIRED PUBLICITY

To the Editor of THE LANCET

SIR,—What is undesired publicity? If the effect of the publicity referred to by your correspondent was to induce the belief that the sulphonamide emanated from British brains, it would no doubt be undesired by the German inventors. If, on the other hand, the effect was to raise from obscurity to the light of day a society known as the British Pharmaceutical Conference, then I do not suppose the publicity would be undesired by that society. It all depends upon the point of view.

I am, Sir, yours faithfully,
F. C. GOODALL.

Whitehall-place, S.W., August 14th.

To the Editor of THE LANCET

SIR,—One of the most advertised events in the history of the world was King Canute's attempt to stop the tide coming in. That ancient ruler has his disciples in many walks of life, all of them, alas, equally unsuccessful. If your correspondent Mr. T. E. Lescher aspires to control the newspaper press of this country the task before him is as hopeless as that which King Canute essayed. May I suggest, however, that it is a simpler matter to control desired publicity than to stop undesired publicity. Also, as a member of the council of the Pharmaceutical Society of Great Britain, under whose ægis the British Pharmaceutical Conference has its being, I think it should be placed on record that it is wholly contrary to the wishes of the conference that the fact that the discovery of the sulphonamides was made in Germany by German chemists should be concealed.

I am, Sir, yours faithfully,
F. W. YEOMANS.

Sparkhill, Birmingham, August 16th.

*** The sulphonamide group has just been added to the list of synthetic products subject to customs duty at the rate of 33⅓ per cent. ad valorem under the Safeguarding of Industries Act.—ED. L.

TAR OR JUST DUST?

To the Editor of THE LANCET

SIR,—In the kindly reference in your last issue to my research on the effects of tar dust and dust minus tar upon the incidence of lung tumours in mice, rather more emphasis is placed upon the effects of the tar than the results of my research indicate. Certainly tar in the dust is an important factor but so is the road dust minus the tar. Thus in the controls the percentage with lung tumours is 20. Special dusting with road dust minus tar produces lung tumours in a further 25 per cent. of the mice with increase in malignancy, while special dusting with road dust containing tar causes an additional effect representing a further increase in incidence in 29 per cent. This gives a total of 20, plus 25, plus 29 per cent., or 74 per cent. with the tar dust, but 25 of the 54 per cent. increase over the control figure (20) is independent of the tar. My opinion as stated in the paper is that road dust minus tar is also an important factor in the ætiology of lung cancer in susceptible individuals, and I hold that the presence of lung tumours in the control mice is also due to an "irritant" inhaled in atmospheric dust which is present everywhere and has to be removed from furniture every day with a duster. We are now testing each ingredient of the dust, commencing with silica, with the view to detecting the carcinogenic factor in the road dust minus tar.

My research is concerned mainly with the ætiology of lung tumours and only indirectly with the question as to whether there is or is not a recent increase in human lung cancer. Sooner or later the results from experiments on animals will be brought into line with data for human diseases, and I hold that already there is much in common as regards pathology and ætiology of lung tumours in mice and men.

Another minor point: the metastases with the dust minus tar as recorded in my paper were in the heart and kidney, not in the liver as stated in your annotation.

I am, Sir, yours faithfully,
J. ARGYLL CAMPBELL.

National Institute for Medical Research, N.W., August 17th.

THE SERVICES

ROYAL NAVAL MEDICAL SERVICE

Surg. Lt.-Comdr. W. P. E. MacIntyre to be Surg. Comdr.

Surg. Lt.-Comdrs. A. M. L. Smith to *Victory* for R.N.B. and to *Glasgow* (on commg.); T. F. Barlow to *Dolphin*; M. A. Graham-Yooll to *Pembroke* for R.N.B.

Surg. Lt.-Comdr. (D) T. G. A. G. Emberson to *Norfolk II.*

Surg. Lt. S. J. Wheeler to be Surg. Lt.-Comdr.

Surg. Lts. P. G. Stainton to *Victory* for R.M. Infirmary, Portsmouth; and J. W. Caswell to *Victory* for R.N.B.

Surg. Lts. (D) S. R. Wallis to *Caledonia* and F. R. M. Willis to *St. Vincent.*

To be Surg. Lts. (D): D. C. Howe and W. G. Smith.

The following appointments as Admiralty Surgeons and Agents have been approved: Mr. C. F. Fairlie, Blyth; Mr. H. P. Clark, Clacton-on-Sea; Mr. G. W. Oliphant, Bridport; and Mr. J. B. Miller, Glasgow.

ROYAL NAVAL VOLUNTEER RESERVE

Surg. Lt. R. M. Heggie (proby.) to *Courageous.*

Surg. Sub-Lt. Gerard Sutherland Irvine promoted to Surg. Lt. (seny., July 30th) and appointed to *Newcastle* (August 2nd).

ROYAL ARMY MEDICAL CORPS

Capt. D. R. W. Burbury to be Maj.

Short Service Commission: Lt. (on prob.) O. Jordan is secd. under the prov. of Art. 213, Royal Warrant for Pay and Promotion, 1931.

REGULAR ARMY RESERVE OF OFFICERS

Lt.-Col. M. B. H. Ritchie, D.S.O., O.B.E., having attained the age limit of liability to recall, ceases to belong to the Res. of Off.

ARMY DENTAL CORPS

Short Service Commission: Lt. H. M. Barbour to be Capt.

TERRITORIAL ARMY RESERVE OF OFFICERS

Maj. E. J. G. Glass to be Maj.

Capts. R. W. Hendry and E. J. B. Sewell, from Active List, to be Capts.

ROYAL AIR FORCE

Squadron Leader E. Thompson to Home Aircraft Depôt, Henlow.

Flight Lt. F. H. Peterson to Central Medical Establishment, London.

Flying Offrs. D. W. I. Thomas and E. J. Moynahan promoted to rank of Flight Lts.

Flying Offr. J. D. H. Cran resigns his short service commission.

Dental Branch.—Flying Offr. A. J. Clegg to R.A.F. Station, Andover.

INDIAN MEDICAL SERVICE

Maj.-Genl. E. A. Walker, C.B., K.H.S., retires.

Capts. to be Majs.: T. A. Malone and W. T. Taylor.

Indian Medical Department.—Asst. Surg. (1st Cl.) C. C. G. O'Reilly to be Lt. (Sen. Asst. Surg.). Lt. (Sen. Asst. Surg.) J. P. Pereira retires.

DEATHS IN THE SERVICES

Brevet Colonel JAMES JOHN PRATT, whose death occurred in London on August 12th, was a very popular member of the Indian Medical Service. A student at Westminster Hospital he graduated M.R.C.S. Eng. in 1881, and entered the I.M.S. two years later after taking the Herbert prize and the Montefiore medal at the Army Medical School. In 1884 he served with the Zhob Valley expedition. He was then for a time at the Naini Tal asylum, and from 1890 on he was civil surgeon at various stations in the United Provinces, and later at Lucknow, where he was medical officer to the volunteer rifles. Retiring in December, 1912, he was appointed examiner of surgical instruments to the India Store Depôt, and was given charge of beds at the Seamen's Hospital Society, lecturing on tropical diseases at the Westminster Hospital and the London School of Tropical Medicine. During this long period he was one of the most regular attenders of the annual dinner in London of the I.M.S. where his voice was often heard.

Col. THOMAS EVELYN FIELDING, whose death occurred at Hindhead on August 9th, was born in 1873, and educated at Trinity College, Dublin, where he qualified in medicine in 1897. He entered the R.A.M.C. in 1900, and served in the South African war, being mentioned in dispatches and awarded the several medals. In the European war he was assistant director of medical services first to the 3rd Division and later to the 28th, commanding a field ambulance and a general hospital. He was thrice mentioned in dispatches and was awarded the D.S.O. in 1915. He married in 1913 Isabel Orpen, daughter of Dr. Benjamin Palmer, of Newry, co. Down.

PANEL AND CONTRACT PRACTICE

Refresher Courses

THE Minister of Health has now stated explicitly the conditions under which he will approve grants for post-graduate study to insurance practitioners. The grants hitherto available for rural practitioners will be continued for the remainder of the present year after which they are to be merged in the larger scheme. The conditions of eligibility are now:

(*a*) That five years have elapsed since the date of first registrable qualification.

(*b*) That the practitioner has not less than 300 (or in the case of a rural practice 150) insured persons on his list.

(*c*) That no grant will be payable more than once in five years.

The grant will include a fee for the course, travelling and subsistence expenses, and the payment of a whole-time locum tenens where necessary. For the present year the arrangements will be limited so far as England is concerned to courses, held in September, October, and November, at the British Postgraduate Medical School at Hammersmith or at other institutions associated with it.

Another Dental Hæmorrhage

A further case in which an insurance doctor was called in to treat hæmorrhage following dental extraction in the absence of the dentist who pulled out the tooth has come up before an insurance committee, this time in the provinces. It will be remembered that in a previous case [1] the practitioner gave the necessary treatment, but as he did not think the treatment ought to be within the scope of medical benefit, which in fact it was, he charged the patient ten shillings. In the recent case the patient went to her doctor who on examination found that she was suffering from arterial bleeding. He tried packing the socket with cotton-wool and adrenaline, and as this was not effective the question of a stitch arose. The doctor told the patient that he had not the material for that sort of work and that she must try and find her own or some other dentist, failing which she might apply for treatment at a local hospital. The patient consulted another doctor who inserted three stitches and made two subsequent visits, one on the following morning and the other a week later, and charged a guinea for his services. When he appeared before the medical service subcommittee the first practitioner said that even if he had had absorbent catgut by him he would not have tackled the job without assistance. (The assistance given to the other practitioner was actually rendered by relatives of the patient.) The insurance committee recommended the Minister to withhold two pounds with a view to a corresponding deduction from the practitioner's remuneration, and decided to refund to the patient the sum of one guinea for expenses incurred. The practitioner appealed against this decision on the grounds that in his judgment treatment could not in the interests of the patient be properly undertaken in his surgery, and that he had fulfilled his duty to the patient in giving her advice. The appeal was heard on May 31st. The practitioner said that he himself could not have undertaken to stitch the gum for lack of proper material and adequate assistance. He had not in his surgery at the time, though he had procured since, a supply of absorbent catgut which was the only suitable material for the purpose. Regarding assistance, the help of another medical man or at least of a trained nurse would have been desirable for swabbing the patient's mouth to expose to view the bleeding point and for preparing for the operation. He thought the patient was going direct to hospital from his surgery, but did not give her a note to take with her as the condition was evident. The legal representative of the practitioner argued that this was a case to which Clause 9 (1) of the Terms of Service should be applied—i.e., the clause that makes it the doctor's duty to advise the patient as to the steps to be taken in order to obtain treatment not within the scope of the practitioner's obligations. It was not contended, however, that the treatment required was outside the practitioner's obligations under the Terms of Service, and the tribunal took the view that the

[1] See *Lancet*, 1936, **1**, 1090; 1937, **1**, 345 and 1549.

clause invoked therefore could not under any circumstances be relevant. There was no provision which enabled the practitioner to discharge his duty by advising the patient as to the steps which she should take in order to obtain treatment which was within the scope of his obligations. Clause 11 (1) provides that a practitioner unwilling to render any particular service may make arrangements with a colleague to act as his deputy; but it is for him to ensure that there is no breakdown. The Minister on consideration of the report of the appeal tribunal dismissed the appeal.

OBITUARY

JOHN GORDON THOMSON, M.B. Edin., F.R.C.P. Lond.

WE regret to announce the death on August 13th of Prof. J. G. Thomson, director of the department of protozoology at the London School of Hygiene. Born at Whitburn, Linlithgowshire, in 1878, the son of William Thomson, a fellow of the Education Institute of Scotland, John Gordon Thomson was educated at the Bathgate Academy and at Edinburgh University where he took his M.A. in 1903. Five years later he graduated in medicine, after gaining distinction in physiology and acting as prosector to D. J. Cunningham. He spent two years in house appointments at the Camberwell Infirmary and then went to Liverpool as Durning-Lawrence research student in tropical medicine. He became pathologist to the Royal Southern Hospital, honorary assistant physician to the Liverpool Chest Hospital, and Beit memorial research fellow. At that time he was contributing to the *Tropical Diseases Bulletin* the sections on malaria and communicating frequently to the proceedings of the Royal Society of Tropical Medicine. In one of these he collaborated with Ross on the employment of enumerative methods, in another with Faulham on periodic variations in the occurrence of trypanosomes, and again with D. Thomson on the cultivation of human tumour tissue in vitro. In 1914 he was appointed lecturer at the London School of Tropical Medicine but on the outbreak of war was soon sent to Egypt where he specialised in pathology and protozoology at Alexandria. He also was engaged in research on the dysenteries prevalent in Gallipoli, and a companion of this period writes of his passionate zeal in his task and his indignation against avoidable suffering. His devotion made a deep impression on all who were associated with him.

Returning to England to take charge of the malaria research laboratory at the War Office he was appointed to the chair of protozoology at Keppel-street when the school was opened in 1918. Here he also undertook the teaching of hæmatology and the pathology of protozoal diseases in man, with the aim of grounding the tropical practitioner in the essentials of his work whether as clinician, hygienist, or laboratory worker. This required the collection and maintenance in his department of cultures and strains of spirochætes, trypanosomes, and other pathogenic and non-pathogenic organisms in order to provide a supply of blood films adequate for teaching purposes. Nevertheless he was able to continue his expeditions abroad, visiting Nyasaland in 1934 when he worked with W. A. Lamborn on the rôle played by hæmatophagous flies in the transmission of various parasites, and conducting a malaria survey on native children. In the following year at the request of the League of Nations he visited Singapore to give a series of lectures, at the same time collecting valuable material from malaria, yaws, and other cases. He twice visited Rhodesia where his researches on blackwater fever added to our basic knowledge of this disease, and for a time he was exchange lecturer in protozoology at Johns Hopkins. His colleagues at the London School valued him for a directness of approach to medical problems and a grasp of essentials which made his advice much sought after, and just as was the case during his war service he was universally popular for he never spared himself where he could help others in their work. There was in fact latterly, as Sir Rickard Christophers has remarked, an almost constant succession of visitors of all nationalities to his department.

Prof. Thomson married Hilda, daughter of Mark Burgess of Alderley Edge, Cheshire, and leaves his widow with a son and daughter.

WILLIAM MELROSE CUMMING, M.D. St. And.

THE untimely death is announced of Dr. William Cumming, lecturer in the department of bacteriology in University College, Dundee. He succumbed to an attack of pneumonia at the age of 39. Educated at the University of St. Andrews he graduated there in medicine in 1922, later taking his M.D. and the public health diploma. He early interested himself in tuberculosis and held appointments at the Grove Park hospital, at Lee, and the Fife and Kinross joint sanatorium. His work on pseudohæmolytic streptococci isolated from sputum in pulmonary tuberculosis was published in the *Journal of Pathology and Bacteriology*, followed by an account of 14 new English cases of pulmonary tuberculosis due to the bovine type of bacillus. More recently he was in charge of the Bradford city sanatorium at Grassington and resigned in order to carry out further research at Dundee. His wife died three years ago and he leaves a son and a daughter.

PEASLEY CROSS ISOLATION HOSPITAL, ST. HELENS.—The Mayor of St. Helens has opened a new cubicle block here, providing accommodation for 10 patients, 5 male and 5 female. It is divided into three single cubicle wards, with a double ward on each side. The glass cubicle system has been adopted.

MEDICAL CHARITABLE SOCIETY FOR THE WEST RIDING.—This society, which was started in 1828, held its 109th annual meeting at Harrogate under the presidency of Dr. W. Edgecombe. These meetings are held in rotation at various centres in the West Riding of Yorkshire, and the work of the society, which helps the widows and other dependants, especially the children, of deceased members who have been unable to make adequate provision for them, is carried out with the coöperation of stewards in the various districts. The financial condition of the society is sound; the invested funds stand at the nominal value of £55,500, and about £100,000 has been given in grants. The annual subscription is one guinea, and the membership is now 1261. At the end of the annual meeting Dr. Wardrop Griffith who is retiring from the treasurership after serving for 16 years, during which time the membership of the society has gone up from 862 to 1261, was presented by the officers and stewards with an antique silver loving-cup. He is succeeded by Mr. Harold Collinson, to whom communications should now be addressed.

MEDICAL NEWS

Medical Society of London

This society has issued its programme for the first half of the session 1937–38. The presidential address on Oct. 11th will be given by Mr. J. E. H. Roberts on sick nursing, past, present, and future. On Oct. 25th Dr. George Graham will open a discussion on treatment by intravenous infusion, to be followed by Mr. G. Gordon-Taylor and Dr. H. I. Coombes. On Nov. 8th Sir Joseph Barcroft, F.R.S., Lord Burghley, M.P., Dr. Adolphe Abrahams, and Mr. A. E. Porritt will take part in a discussion on national physical training. And on Dec. 13th Mr. H. W. Rodgers, Dr. G. T. Calthrop, and Dr. S. Cochrane Shanks will discuss modern methods of investigating gastric diseases. Next year Dr. Graham will survey in his Lettsomian lectures the changes and results of treatment in diabetes in the last 15 years; the annual oration will be delivered on May 9th by Sir Henry Gauvain on planning a hospital.

Chartered Society of Massage and Medical Gymnastics

The annual congress of this society will be held this year from Sept. 20th–24th. The dinner will take place on Sept. 22nd at the Café Royal, Dr. James Mennell presiding, and the lecture given annually in honour of the founders of the society on Sept. 24th. This lecture is being given this year by Mr. H. A. T. Fairbank on unusual causes of backache. At the congress the opening lecture is by Prof. G. R. Girdlestone on the treatment of scoliosis, and the other medical lecturers will include: Miss Maud Forrester-Brown on physiotherapy in the treatment of injuries; Mr. K. L. Parsons on treatment by manipulation; Mr. Lawrence Abel on the surgery of the sympathetic nervous system; Mr. J. S. Yates-Bell with Dr. S. S. Cooksey on faradism and pelvic floor exercises for urinary incontinence; Dr. A. T. Todd on the treatment for chronic rheumatism; Dr. Noel Harris on hysteria; Dr. Doris Odlum on psychological factors in physical diseases; Mr. J. H. Seddon on the application of occupational therapy to orthopædic conditions; Dr. W. S. C. Copeman on chronic rheumatism; Mr. A. E. Porritt on ruptures, ancient and modern; Prof. E. W. Hey Groves on intracapsular fractures; Mr. A. W. Adams on orthopædic and other operations under spinal anæsthesia; Dr. J. Kalnanson on indications for short wave therapy; Dr. Clement Nicory on the importance of the physical therapeutist in preventive medicine; Dr. R. L. Kerr on remedial exercises in the treatment of abnormalities of binocular vision and asthenopia. Tickets of admission to any of these lectures will be sent to medical men applying to the secretary of the society at Tavistock House, Tavistock-square, London, W.C.1.

Central London Throat, Nose, and Ear Hospital

The annual address will be given on Oct. 8th, 1937, at 4 P.M. by Sir StClair Thomson on subglottic intrinsic cancer of the larynx.

North Devon Hospital

A new nurses' home is shortly to be erected here and the present nurses' accommodation is to be converted into a medical ward and isolation ward for women. A special appeal for funds for this purpose will presently be issued.

Fellowship of Medicine and Post-Graduate Medical Association

Courses in physiology and in anatomy and embryology in preparation for the F.R.C.S. (primary) examination will be given on Monday, Wednesday, and Friday evenings, at 5.30 P.M. and 8 P.M. respectively, from Sept. 1st to Nov. 22nd. Courses suitable for M.R.C.P. and M.D. candidates will be as follows: clinical and pathological at the National Temperance Hospital, Tuesday and Thursday evenings at 8 P.M., Sept. 7th to 23rd; chest and heart at the Royal Chest Hospital, Mondays, Wednesdays, and Fridays, at 8 P.M., Sept. 13th to Oct. 2nd; chest diseases at the Brompton Hospital on two afternoons weekly, at 5 P.M., from Sept. 6th to Oct. 2nd; neurology at the West End Hospital for Nervous Diseases in the afternoons from Sept. 20th to Oct. 2nd. A course, suitable for D.C.H. candidates, will be given at the Infants Hospital, occupying the whole of each day from Sept. 20th to 25th. A two-day course in plastic surgery will be given on Wednesday and Thursday, Sept. 15th and 16th. A course in proctology will be held at the Gordon Hospital from Sept. 27th to Oct. 2nd, and a week-end course in ophthalmology at the Royal Westminster Ophthalmic Hospital on Saturday and Sunday, Sept. 25th and 26th. Detailed syllabuses may be obtained from the Fellowship of Medicine at 1, Wimpole-street, London, W.1. Courses are open only to members.

Société Internationale de Chirurgie

The eleventh congress of this society will be held in Vienna from Sept. 19th–22nd, 1938, under the presidency of Prof. Rudolph Matas of New Orleans.

New Hospital for Halesowen

The trustees of Halesowen Cottage Hospital have decided to accept the offer of Mr. Somers, president of the hospital and charities committee, to give a portion of the Grange Estate as a site for a more up-to-date hospital. Mr. Somers is also giving £10,000 towards the cost of the new building.

THE LANCET 100 YEARS AGO

August 19th, 1837, p. 751.

From an abstract of a report in "The Dublin Journal," July, of Dr. S. Bigger's experiments on Transplantation of the Cornea, to relieve Blindness, hitherto deemed incurable.

On his return to Dublin, Dr. Bigger commenced his experiments anew; of these, he has now performed eighteen. The subjects of the first and last experiments, two rabbits, were presented before the King and Queen's College of Physicians, on the 18th of May last, and the degree of vision which one of them evidently possessed, reflects the highest credit on the operator. Of these eighteen experiments, in ten, the iris was injured; in eleven, the crystalline lens escaped; in seventeen, union took place between the implanted corneæ and the adjacent surfaces in forty-eight hours, so as to admit of the withdrawal of the ligatures, which are always a great source of irritation; in four, three ligatures were employed; in fourteen, only two, and with equally favourable results; in twelve, adhesion of the iris to some part of the cicatrix ensued; in one, sloughing of the cornea and destruction of the eye took place, an event which arose from the cornea being kept for half an hour without applying it, with the view of ascertaining how long it would be likely to retain a sufficient degree of vitality to enable it to unite, a delay which may be prejudicial to the operation. Of the whole eighteen, sixteen recovered imperfect vision.

The difficulty of preserving the transparency of the implanted cornea, was constant until his ninth experiment at home, when Dr. Bigger discovered that much benefit might be derived from the local application of bichloride of mercury. A weak solution, gradually increased to three grains to the ounce of distilled water, dropped into the eye three or four times a day, after the cornea had become adherent, was found to exercise an almost specific action in diminishing the opacity of the implanted cornea. Iodine and nitrate of silver had improved the appearance of the cicatrix, but did not act upon the milky state of the cornea. The corrosive sublimate must be begun with a weak solution, and not used until the implanted cornea is perfectly united to its new connexions.

A footnote to this report says:—

The first time Dr. Bigger tried this experiment was in 1835, when he was a prisoner with a tribe of Arabs, on a journey from Grand Cairo. A pet gazelle had lost one eye from inflammation, and the power of seeing with the other, from a wound of the cornea. The cornea was taken from another animal of the same species, brought in wounded but not quite dead; adhesion took place, and in ten days the animal gave unequivocal signs of vision, the upper part of the transplanted cornea remaining perfectly transparent.

Appointments

EAGER, RICHARD, M.D. Aberd., Consultant in Psychiatry to the Royal Devon and Exeter Hospital.

HESLOP, J. F., M.B. Manch., F.R.C.S. Eng., Resident Surgical Officer at the Manchester Royal Infirmary.

TUNBRIDGE, R. E., M.D. Leeds, M.R.C.P. Lond., Honorary Physician to the Leeds Public Dispensary and Hospital.

WRAGG, A. W., M.R.C.S. Eng., Senior Resident Medical Officer to the Taunton and Somerset Hospital.

Certifying Surgeons under the Factory and Workshop Acts: Dr. J. GROCOTT (Hanley District, Stafford); Dr. T. J JONES (Talybont District, Cardigan).

Vacancies

For further information refer to the advertisement columns

Aberdeen University.—Crombie-Ross Lectureship in Psychopathology, £650.
Albert Dock Hosp., Connaught-road, E.—Res. M.O., at rate of £110.
Barnstaple, North Devon Infirmary.—Res. M.O., £150.
Bath and Wessex Children's Orthopædic Hosp., Combe Park.—H.S., at rate of £120.
Birmingham, Dudley-road Hosp.—Jun. M.O., at rate of £200.
Birmingham, Royal Cripples Hosp.—Res. H.S., at rate of £200.
Bolton Royal Infirmary.—H.S., at rate of £150.
Bradford Municipal General Hosp., St. Luke's.—H.P.'s and H.S.'s, each at rate of £150.
Brighton, New Sussex Hosp. for Women, Windlesham-road.—Hon. Surgeon.
Brighton, Royal Sussex County Hosp.—H.S., £150.
British Postgraduate Medical School, Hammersmith.—H.S. (Obstetrics), at rate of £105. Also Res. Anæsthetist and Cas. O., each at rate of £150.
Caithness County Council.—Surgical Specialist, £1000.
Cambridge, Addenbrooke's Hosp.—H.S., at rate of £130.
Canterbury, New Kent and Canterbury Hosp.—H.S., at rate of £125.
Cardiff, King Edward VII Welsh National Memorial Association. Area Asst. Tuber. Phys., £500. Res. M.O., £350. Two Asst. Res. M.O.'s, each £200. Also three Half-time Asst. Tuber. O.'s, each £250.
Cardiff Royal Infirmary.—H.P.'s, H.S.'s, and Cas. Surg. O., each at rate of £50. Also Ophth. H.S., at rate of £80.
Chelmsford Borough.—M.O.H. and School M.O., £800.
Colchester, Royal Eastern Counties Institution, &c.—Asst. M.O., £400.
Derby, Derbyshire Royal Infirmary.—Gynæcological H.S. and Emergency Anæsthetist, £150. Also H.S., £150.
Derbyshire Education Committee.—Asst. School M.O., £500.
Devonport, Prince of Wales's Hosp.—Sen. H.S., at rate of £130.
Dreadnought Hosp., Greenwich, S.E.—H.S. and H.P., each at rate of £110.
Eastbourne, Princess Alice Memorial Hosp.—Third Hon. Anæsthetist.
Glasgow Royal Samaritan Hosp.—Visiting Surgeon.
Guildford, Warren-road Hosp.—Res. Asst. M.O., at rate of £375.
Halifax Royal Infirmary.—Res. Surg. O., £250.
Herefordshire General Hosp.—H.S. and Cas. O., £100.
Huddersfield Royal Infirmary.—Cas. O., at rate of £200.
Ilford Borough.—Asst. Dental Surgeon, £450.
Jewish Maternity Hosp., Underwood-street, E.—Res. M.O., at rate of £50.
King Edward Memorial Hosp., Ealing.—H.S. to Spec. Depts., at rate of £150.
Kingston-on-Thames, Surrey County Hosp.—Res. Obstetrician, £725.
Leamington Spa, Warneford General Hosp.—Res. Jun. H.S. and Cas. O., at rate of £150.
Leeds City.—Asst. M.O., £500.
Leeds Hosp. for Women.—Hon. Anæsthetist.
Leicester City Mental Hosp., Humberstone.—Deputy Med. Supt., £800. Also H.P., at rate of £300.
Leicester Royal Infirmary.—Res. Anæsthetist, at rate of £150. H.S., two H.P.'s, Sen. Cas. O., each at rate of £125. Also Jun. Cas. O., at rate of £100.
Liverpool Sanatorium, Delamere Forest, Frodsham.—Sen. Asst. to Med. Supt., £350. Also Jun. Asst. to Med. Supt., £225.
Lochgilphead, Argyll and Bute District Mental Hosp.—Res. Asst. M.O., £300.
London County Council.—Coroner for the County of London, £1700. Asst. M.O.'s, Grade I, £350. Also Grade II, £250.
Maidstone, Kent County Ophthalmic and Aural Hosp.—Sen. and Jun. Ophth. H.S.'s, at rate of £250 and £200 respectively.
Manchester, Ancoats Hosp.—Asst. Pathologist, £300 to £350.
Manchester, Duchess of York Hosp. for Babies.—Sen. and Jun. Res. M.O.'s, at rate of £125 and £75 respectively.
Manchester Ear Hosp.—Res. H.S., £120.
Manchester Royal Children's Hosp., Pendlebury.—Asst. M.O. for Out-patients' Dept., at rate of £150.
Manchester Royal Infirmary.—Asst. M.O. to Massage and Electrical Dept., £100.
Melbourne University.—Chair of Anatomy, £1200.
Norwich, Norfolk and Norwich Hosp.—Res. Surg. O., £250.
Nottingham City.—Asst. Tuber. O., £500.
Perth City.—M.O.H., £800.
Preston, Biddulph Grange Orthopædic Hosp.—Jun. H.S., at rate of £200.
Preston and County of Lancaster Royal Infirmary.—H.S. to Eye, Ear, Nose, and Throat Dept., at rate of £150.
Preston, Wrightington Hosp., Appley Bridge.—Jun. Asst. M.O., £200.
Prince of Wales's General Hosp., N.—Res. Jun. H.P. and two Res. Jun. H.S.'s, each at rate of £90.
Princess Elizabeth of York Hosp. for Children, Shadwell, E.—H.P., at rate of £125.
Princess Louise Kensington Hosp. for Children, N. Kensington, W. Clin. Asst.
Queen's Hosp. for Children, Hackney-road, E.—Res. M.O., at rate of £200. Also H.P. and Cas. O., each at rate of £100.
Reading, Royal Berkshire Hosp.—R.M.O. to Blagrave Branch, at rate of £150.
Rochdale Infirmary and Dispensary.—Second H.S., at rate of £150.
Rotherham Hosp.—Sen. H.S., £200. Also H.S. for Ophth. and Ear, Nose, and Throat Depts., £150.
Royal Cancer Hosp., Fulham-road, S.W.—Two Asst. Radiologists, each £350. Also H.S., at rate of £100.
Runwell Hosp. for Nervous and Mental Disorders, near Wickford, Essex.—H.P., at rate of £150.
Ryde, Royal Isle of Wight County Hosp.—Hon. Surgeon to Ear, Nose, and Throat Dept.
Salop County Council (Medical Inspection of School-children and Maternity and Child Welfare Schemes).—Asst. M.O., £500.
Salvation Army Mothers' Hosp., Lower Clapton-road, E.—Sen. Res. M.O., £150.
Sheffield, Jessop Hosp. for Women.—Res. M.O., at rate of £150.
Sheffield Radium Centre.—Locum Tenens M.O.
Sheffield Royal Infirmary.—Cas. O., at rate of £150.
Shrewsbury, Royal Salop Infirmary.—Res. Surg. O., £250. Also Res. H.S., at rate of £160.
Southampton, Royal South Hants and Southampton Hosp.—Cas. O., and Res. Anæsthetist and H.S. to Ear, Nose, and Throat Dept., each at rate of £150.
Stafford, Staffordshire General Infirmary.—H.S., at rate of £200. Also H.P. and Cas. O., at rate of £150.
Stoke-on-Trent, Longton Hosp.—H.S., at rate of £180.
Stoke-on-Trent, North Staffs Royal Infirmary.—Second H.P., at rate of £150.
Swansea General and Eye Hosp.—H.P., at rate of £150.
Tunbridge Wells, Kent and Sussex Hosp.—H.S. to Ear, Nose, and Throat Dept., £150.
Wakefield City.—Jun. Asst. M.O., £500.
Wakefield, Clayton Hosp.—Two H.S.'s, each at rate of £200.
Wakefield, Scalebor Park Mental Hosp.—Asst. M.O., £650.
Warwick, King Edward VII Memorial Sanatorium, Hertford Hill.—Jun. Asst. M.O., at rate of £250.
West Bromwich, Hallam Hosp.—H.P. and H.S., each at rate of £200.
West London Hosp., Hammersmith-road, W.—Res. Anæsthetist, at rate of £100.
Weston-super-Mare General Hosp.—Res. H.P., £150.
Wigan, Royal Albert Edward Infirmary and Dispensary.—Res. Med. and Surg. O. and Reg., £250. Also two H.S.'s, each at rate of £150.
Windsor, King Edward VII Hosp.—Res. M.O., £200.
Wolverhampton, Royal Hosp.—H.P., at rate of £125.
Worcestershire Mental Hosp., Barnsley Hall, Bromsgrove.—Second Asst. M.O., £350.

The Chief Inspector of Factories announces a vacancy for a Certifying Factory Surgeon at Cross Hills (York, W. Riding).

INDEX TO "THE LANCET," VOL. I, 1937

THE Index and Title-page of Vol. I, 1937, which was completed with the issue of June 26th, is now ready. A copy will be sent gratis to subscribers on receipt of a post-card addressed to the Manager of THE LANCET, 7, Adam-street, Adelphi, W.C.2. Subscribers who have not already indicated their desire to receive Indexes regularly as published should do so now.

REST ROOMS AT ST. BARTHOLOMEW'S.—More accommodation for visitors to patients ill enough to require their attendance through the night has been provided in the new medical block opened recently by Queen Mary. The original sleeping accommodation has been doubled and there are now 12 cubicles for women and 10 for men. Each has a divan and an armchair, and a canteen is open all night.

WALLSEND INFIRMARY.—A tender for extensions, which include a new maternity block, has been provisionally accepted and the commissioner for special areas has made a grant of 75 per cent. towards the scheme. The cost has been estimated at about £12,750, and various donations have already been offered. It is thought that an added annual income of about £2000 will be needed when the extensions are complete.

NOTES, COMMENTS, AND ABSTRACTS

"CHYRURGIC MEMOIRS"

BY ENID WILLIAMS, M.D.

John Moyle, senior, "one of Her Majesties Antient Navy Chirurgions," published in the year 1708 a book entitled "Chyrurgic Memoirs." It was dedicated to Prince George of Denmark and consists of an account of "many Extraordinary Cures which occurred in the Series of the Author's Practice especially at Sea."

Fifty-four cases are described with a vivid detail often lacking from modern case reports. A short preface, whose naïveté and sincerity arrests attention, promises to "shew . . . the Practical Part of Chyrurgery Pithily. And wherein through unadvisedness I made any false Steps, I have here ingeniously shewed them as PHARI to caution you." Actually it is not until page 75 that he records a failure, not in a major feat of surgery, but an autopsy on a gentlewoman of 32 who had suffered from a "stupendious Hydrops." He ingeniously confessed that he knew not her distemper and was not willing to tamper with what he did not understand. "But opened she was." From the description of his findings it appears likely that the condition was an immense ovarian cyst. This is the only case he failed to cure; he shelved the responsibility and made the excuse that he was only an interested neighbour! All the others were alleged to have been cured by his skill. The notes are written in a happy narrative style as: "Two of the gunroom crew falling out, one happened to receive an unlucky blow on the head with a hand-spike" (p. 22). "Two men differing in heaving of Ballest, the one gave the other a violent blow with his Shovel on the side of the Head" (p. 34). "Being in Spain a Spaniard with his Stilletto stabbed one of our men in the back" (p. 62).

Among the cases described are ten of head injuries, four of which were trepanned to evacuate submeningeal hæmorrhages or to raise depressed fractures. There are ten notes of wounds and injuries with hæmorrhage, and eight are devoted to syphilis and other venereal conditions. Operations were carried out with the assistance of the crew aboard and the patient received a "Cordial to keep up his spirits." Hæmorrhage was controlled by tourniquet, the cauterising button, and by styptics such as powdered toad or dragon's blood. When Moyle amputated a limb he used "dossels of Stupa sicca for the end of the bone." He stitched the skin with thread and after removing the stitches liked the wound to "digest kindly"—which it probably always did and then healed by granulation. He was quite pleased when the stump was "red as a cherry" and the bone exfoliated. Healing then took place after dressings of wine stupes and other mysterious ingredients had been applied. Hæmorrhage was treated heroically; he tells of a man bleeding from the nose who "resisted all common means . . . but the hæmorrhage still continuing and the man was like to bleed to death, at length I was sent for. I immediately opened the cephalic vein in the Cutulus of the Arm." He then "blowed up into the Nostrils" the following powder: "R. Pulv. ex. Carm. Bufon. Bol. Ver. Ana. ℥ii Misce." The patient was put to bed with a draught of 40 drops of laudanum in a glass of beer, and was advised to refrain from "Capital Liquors" and to drink small beer in future.

The memoirs on syphilitic and venereal conditions include descriptions of gummata, periosteal nodes, penetrating ulcers of the cranium, "sordid ulcers," as well as buboes and primary sores. Mercury was his sheet anchor in treating them. Moyle pushed the mercury, orally and by inunction, until the patient salivated two quarts in 24 hours. This salivation was maintained for three weeks and purging was carried out at the same time. He was convinced of the value of this régime, believing that the body excreted the mercury and the "siphylic venom" at the same time. Although his drugs now seem fantastic and his judgment strangely opposed to what we would call sound common sense, John Moyle supplies good reasons for his actions at every step. Whether he was treating what he called squinzy, dislocated amygdals, apostems or any other "vexatious evils" with all the curious fairy-tale drugs of his age, his practice was mostly the result of personal experience, but he was not afraid of experiment once in a while.

A copy of these vivid memoirs were found in the library of the Welsh National Medical School at Cardiff, and I am indebted to Dr. Frank Hawking of the pharmacology department of the school for some of these notes on them.

RECENT WORK ON PELLAGRA

THE varied problems presented by pellagra continues to engage widespread attention. Last year H. S. Stannus showed [1] that quite apart from the countries with a high incidence of endemic pellagra such as Northern Italy, the U.S.A., Rumania, Transcaucasia, and Egypt, the disease occurs sporadically almost in all parts of Africa and in the tropical regions of Asia, Australia, and America, though endemics are confined to institutions and prisons. Stannus also points out that in many cases of undoubted pellagra one or more of the classical triad of symptoms, dermatitis, diarrhœa, and dementia, may be absent, and he makes out a good case for the inclusion under the label of pellagra of some conditions which have been described as different diseases. Stannus has also discussed and criticised the different theories of causation of pellagra. He maintains [2] that there is no difference between pellagra and conditions described as sporadic, pseudo-, para-, alcoholic, and secondary pellagra. The import of the observation by Spies and Payne that Castle's intrinsic factor is secreted by the stomach in pellagra is discussed, and also the association of the liberation of histamine in the skin with the exanthem in pellagra. A new theory of the causation of pellagra is thus developed. Stannus does not regard maize and a specific infective agent as factors in the ætiology of pellagra, nor does he believe the disease to be a simple avitaminosis. He classes it among a number of conditions which are severally attributed to a failure in the production of "principles" by the interaction of "extrinsic factor" in the food with "intrinsic factor" normally produced in the gastric juice. The extrinsic factor is held to include proteins of high biological value and some parts of the vitamin-B_2 complex; the intrinsic factor to be a constituent of the gastric juice which fails to be secreted after gastritis. It is not so easy to follow Stannus's ideas about the action of the anti-pellagrous factor, which he believes to be stored in the liver. He describes the action as that of "a catalyst governing the metabolism of the cells of the skin, mucous membranes and nervous system," and the changes in the tissue cells as "of the nature of a change in the colloid state of their contents towards lessened dispersion of flocculation."

Spies, Chinn, and McLester [3] have treated 50 cases of severe "endemic" pellagra in Birmingham, Alabama, U.S.A., in the following régime: complete rest in bed, a mixed food of very high calorie value (about 900 calories daily from protein, 2000 from fat and 1700 from carbohydrates), and a daily dose of 180–270 g. of powdered brewer's yeast, supplemented in some cases by an intravenous injection of 80–100

[1] Stannus, H. S. (1936) *Trop. Dis. Bull.* **33**, 729, 815, 885.
[2] — (1937) *Ibid*, **34**, 183.
[3] Spies, T. D., Chinn, A. B., and McLester, J. B. (1937) *J. Amer. med. Ass.* **108**, 853.

c.cm. of liver extract. They claim that this treatment reduced the death-rate from 32 per cent. to 6 per cent. and that the fatal cases die not from pellagra but from other diseases, the pellagrous symptoms being improved. At autopsy all those "endemic" pellagrins exhibited severe injuries of the gastro-intestinal tract.

Sydenstricker and Armstrong [4] have reviewed 440 cases of pellagra observed by them in Augusta, Georgia, U.S.A., between Jan. 1st, 1919, and Dec. 31st, 1934. Of this series 8·8 per cent. gave histories of addiction to alcohol. The incidence of pellagra in the different years, the seasonal incidence, the distribution between races, sexes, and age-groups, the death-rate, the occurrence of the clinical symptoms, the incidence of anæmia in pellagra, and the complications are discussed. The most striking results were: that the incidence of pellagra has a high peak in May, June, and July; pellagra was found to occur twice as often in females as in males; about 70 per cent. of the pellagrins were between 21 and 50 years of age; a daily addition of 30–90 g. of dried yeast to the food seems to have reduced the death-rate from 33·7 per cent. to 25·3 per cent. Psychoses and high temperatures were much more common in those patients who died than in those who recovered. Anæmia was found in 83·6 per cent. of the patients, hypochromic anæmia in 77·6 per cent. Most of the patients showed an achlorhydria. Subacute combined sclerosis and peripheral neuritis were rare. Complications with other diseases were found in nearly half of the patients. In a very high proportion of autopsies on fatal cases lesions of the liver, most often fatty degeneration, were found.

Beckh, Ellinger, and Spies [5] report on the incidence of an increased porphyrin excretion chiefly in "alcoholic" pellagrins of Cleveland, Ohio, U.S.A. Ellinger had previously shown with Edgar and Lucas that rats deprived of the vitamin-B_2 complex in the food excrete a highly concentrated porphyrin in the urine which disappears after adding vitamin B_2 to the diet, and with Dojmi that endemic pellagrins in southern Jugoslavia also excrete a highly concentrated porphyrin in the urine. Beckh, Ellinger, and Spies now show that the "alcoholic" pellagrins mostly have also an increased porphyrin excretion which disappears with the clinical symptoms of pellagra on suitable treatment. They discuss the ætiology of this porphyrinuria and its importance in the development of the pellagra, and point out the great similarity between the clinical symptoms of pellagra and of the genuine porphyria.

HEALTHY HOLLAND

COMPARISONS of the death-rates from different causes of death between one country and another are notoriously dangerous. Standards of certification, medical fashions and customs, statistical rules of tabulation all play their part in producing differences in the recorded rates which may or may not bear any relation to the real facts. Total death-rates are a different matter, and in countries of western civilisation with a high standard of registration and reliable (and reasonably frequent) enumerations of their population, comparisons of interest can often be made. One such comparison was made by the Registrar-General for England and Wales in his annual text volume for 1934, where he set out the recently recorded death-rates in broad age-groups in a dozen different countries. A particularly striking contrast is presented by the relative levels of mortality in England and Wales and Holland, a contrast which has been pointed out to us by a medical officer of health. The comparable rates given by the Registrar-General are for the three years 1930–32. In that period the infant mortality-rates in England and Wales were 72 per 1000 live births for males, 55 per 1000 for females. In Holland the comparable figures were only 55 and 42, so that the Dutch rates were nearly one-quarter lower. It is possible that differences in the definition of a stillbirth play some part in the advantage apparently enjoyed by Holland, for according to the Statistical Handbook of the League of Nations' Health Organisation,[1] stillbirths in Holland include a proportion of children born alive but dying before registration—i.e., within 3 days of birth (an example of the dangers of too ready international comparison). But that this is most certainly not the whole explanation is shown by the comparison of the death-rates at later ages.

In the first years of childhood, ages 1–4 years, the death-rates recorded in Holland in 1930–32 were for males nearly a third, and for females fully a third, below those registered in this country. In the broad age-group 5–34 years the equivalent average rate (a standardised rate obtained by taking equal populations in each quinquennial age-group) was in Holland 72 per cent. of the rate in England and Wales for males and 77 per cent. for females. At ages 35–64 the corresponding ratios were 70 and 94, at ages 65–75 they were 79 and 101. It is clearly advantageous to pass the years of childhood in the Netherlands. For the male sex this advantage is not lost up to age 75, but the rates of women grow progressively nearer to those of our own country and even slightly exceed them at ages 65–75. It is a curious position. What causes produce such a relatively low mortality in the males of Holland at ages 35–75 and yet not tell to the advantage of the women? Or is it some factor which bears hardly on English males and not on their wives? At these ages the death-rates of English males are about one-third above the rates of English females, while the rates of the Dutch males and females differ very little. Whether it is the English man or the Dutch woman, or both, who have grounds for complaint it is difficult to say.

If we extend the field of observation we find that the mortality-rate in Holland has declined over the last quarter of a century considerably more than the rate in England and Wales. In 1911–13 the crude death-rates of the two countries did not differ appreciably; they were 13·9 per 1000 in England and Wales and 13·1 in Holland. In 1935 the English rate had fallen to 11·7, the Dutch to 8·7. Changing age constitutions may play a part in this difference and necessitate standardised rates, for over the same period of time the birth-rate in Holland fell less rapidly than the rate in England. But between 1911–13 and 1935 the infant mortality-rate also fell by 62 per cent., that is, faster in Holland than in England and Wales, where the decline was by 49 per cent. The League's epidemiological reports also show the infant mortality-rates in recent years in twenty Dutch towns to have been nearly half the figure registered in the 121 great towns of England and Wales, and the crude death-rates to have been about one-third less. Risking some comparisons of causes of death we find that the death-rates attributed to measles, scarlet fever, and diphtheria have for a considerable period been appreciably less in Holland than in this country. With whooping-cough there is little difference, and influenza takes a nearly equal toll. The tuberculosis death-rate was in 1935 substantially lower in Holland though up to 1927 there was little difference or even a higher rate in the Netherlands. The widening difference between the rates from this cause is of particular interest and seems worthy of inquiry. The League's Statistical Handbook shows that up to 1921 there was a very different trend in the death-rates from pulmonary tuberculosis experienced by the two sexes. In England and Wales the death-rates of males between 1901 and 1921 annually exceeded the rates of females, but the male rate fell rather more rapidly than the female rate. In Holland there was very little

[4] Sydenstricker, V. P., and Armstrong, E. S. (1937) *Arch. intern. Med.* **59**, 883.

[5] Beckh, W., Ellinger, P., and Spies, T. D. (1937) *Quart. J. Med.*, New Series, **23**, 305.

[1] No. 1. The Official Vital Statistics of the Kingdom of the Netherlands, 1924.

difference between the sexes between 1901 and 1903, the male rate being a little the higher; but between 1904 and 1921 the female death-rate was consistently greater and its relative position grew steadily worse. This, in the words of the handbook, "suggests the importance of some novel factor and the desirability of a special enquiry."

The authors also point out that before 1880 the death-rate in the Netherlands from diphtheria and croup was often higher than in England and Wales. This condition persisted until 1890, but since then the rate of mortality in the former has been, as stated already, much less than in the latter. This again suggests a subject for epidemiological investigation. In short, we have two countries, both highly urbanised, both with reliable systems of vital statistics, but with striking differences between the results shown by those statistics. There would seem to be here an interesting subject for study by some medical statistician with a knowledge of the social conditions of both countries.

STUDIES IN THE HISTORY OF MEDICINE

EVIDENCE of the enthusiasm and assiduity with which medical historians in the United States are prosecuting their studies is provided by two slender volumes of great interest.[1 2] The design of the two books is somewhat different: that on Withering may be called a miniature biography with the essence of Withering's best-known work given in his own language: that on Langerhans is a reprint of the original German essay with a translation and a brief account of the life of its author. Of the two commemorated thus probably the name of Langerhans is the more familiar to the medical profession, because it has happened, thanks to the courtesy and sense of justice of a French colleague, that the name has become attached to those cells in the pancreas which later research has proved to be of such high importance in the assimilation of carbohydrates. But Withering's discovery of the value and the use of digitalis was in one sense more complete, for, as Dr. Roddis shows, later research has added but little essential to his accurate and scientific observations, though it has elucidated the mode of action of the drug, and the diuretic effect of its administration which was Withering's chief concern has sunk into insignificance beside its cardiac effects. Yet its effect on the pulse was carefully noted by its discoverer; he remarks "that it has a power over the motion of the heart to a degree yet unobserved in any other medicine, and that this power may be converted to salutary ends."

The two discoveries were separated by almost a century, but it is interesting to recognise the true scientific spirit displayed by the two explorers: Langerhans employing methods of examination which were not at Withering's command, but exhibiting the same instinctive recognition of the unusual and the same careful experiments to test and retest his results. Withering appears originally to have used the turkey for his animal experiments; Langerhans a variety of animals, but chiefly the rabbit and the salamander. Withering had the scientific man's highest reward, to see his work bearing fruit; Langerhans had found he knew not what, but with true scientific modesty recorded what he had observed with the remark that "he must refrain from speculation."

Both these brochures—for they are little more—are excellent specimens of the careful historical work of the American school of medical history; both are excellently produced and will well repay the brief period necessary for their perusal.

[1] William Withering. By Louis H. Roddis, M.D., Commander, Medical Corps, U.S. Navy. New York: Paul B. Hoeber, Inc., Medical Book Department of Harper and Bros. Pp. 131. 9s. 6d.

[2] Contributions to the Microscopic Anatomy of the Pancreas. By Paul Langerhans (Berlin, 1869). Reprint and translation by H. Morrison, M.D. Baltimore: Johns Hopkins Press; London: Humphrey Milford, Oxford University Press. 1937. Pp. 39. 4s. 6d.

CANCER RESEARCH IN MANCHESTER

SHORTNESS of funds has not prevented the Manchester committee on cancer from continuing some interesting lines of research into the incidence of cancer in an industrial neighbourhood. The scientific staff of the committee which is advised by Dr. A. Lasnitzki, formerly of the Berlin Cancer Research Institute, is endeavouring to isolate from dangerous oils the constituents which cause cancer. Determination of the refractive index and of the viscosity of an oil may throw more light on its cancer-producing powers than the skin test, besides being inexpensive and leading to quicker results. Gratifying success is reported from the use of an ointment consisting of lanolin and olive oil in reducing the onset of industrial dermatitis. Especially in the oil-shale industry the workmen have come to appreciate this preventive treatment, finding that the daily use of the mixture changes a rough dry scaly skin to one of smooth and healthy appearance. The agents in the causation of cancer and dermatitis are of course not the same, but similar measures of prevention can deal with both conditions. The committee has received a grant of £1000 for two years from the British Empire Cancer Campaign for the investigation of atmospheric pollution from the exhaust fumes of motor vehicles using heavy oil. These fumes, which are daily on the increase, differ from those of petrol cars in containing far more soot and tar. Dr. Lasnitzki is also investigating the influence on the growth of cells of such cancer-producing agents as are present in tar and mineral oils.

Medical Diary

Information to be included in this column should reach us in proper form on Tuesday, and cannot appear if it reaches us later than the first post on Wednesday morning.

LECTURES, ADDRESSES, DEMONSTRATIONS, &c.

BRITISH POSTGRADUATE MEDICAL SCHOOL, Ducane-road, W.

WEDNESDAY, August 25th.—3 P.M., clinical and pathological conference (surgical).

THURSDAY.—3 P.M., operative obstetrics.

Daily, 10 A.M. to 4 P.M., medical clinics, surgical clinics or operations, obstetrical and gynæcological clinics or operations.

Births, Marriages, and Deaths

BIRTHS

CURRIE.—On August 15th, at Astoria Nursing Home, Colwyn Bay, to Kathleen (née Pilkington), wife of Donald I. Currie, F.R.C.S. Appleton, Conway-road, Colwyn Bay—a daughter.

DALZIEL.—On August 8th, at West Wickham, Kent, the wife of Dr. John Dalziel, of a daughter.

GOGGS.—On August 11th, the wife of Dr. F. N. Goggs, Staines, Middlesex, of a daughter.

HAMAND.—On August 9th, at Reading, the wife of Dr. C. R. Hamand, of a daughter.

HENDERSON.—On August 13th, at Holyport, Berks, the wife of Dr. Leigh H. Henderson, Sudan Medical Service, of a daughter.

WARD.—On August 8th, at Bridlington, the wife of Dr. Gerald Ward, of a daughter.

MARRIAGES

KELLY—GLANVILLE.—On July 31st, 1937, at the Honan Chapel, University College, Cork, John Kelly, M.B., F.R.C.S., to Alice Glanville, M.B.

DEATHS

CHAPLIN.—On August 11th, Ursula Chaplin, M.D. Glasg., L.R.C.P. Edin., of Little Baddow, Essex, aged 67.

ELLIS.—On August 15th, Surg. Capt. Ernest Fitzgerald Ellis, M.R.C.S. Eng., R.N. (retd.), of Bridgnorth.

MACLAREN.—On August 12th, Norman Maclaren, M.B. Camb., F.R.C.S. Eng., of Carlisle.

THOMSON.—On August 13th, Prof. John Gordon Thomson, M.B. Edin., F.R.C.P. Lond.

N.B.—A fee of 7s. 6d. is charged for the insertion of Notices of Births, Marriages, and Deaths.